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LATE EFFECTS OF TOTAL GASTRECTOMY IN MAN*

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STUDIES on patients who have survived total gastrectomy for three years or more are few, and contradictory results are reported. For this reason and since total gastrectomy is being practiced with rapidly increasing frequency, we have studied intestinal motor function, intestinal absorption, pancreatic function and the blood picture in 3 patients who have survived total gastrectomy for three, five and ten years, respectively.¶

CASE REPORTS

CASE 1. E. O., a 58-year-old woman, was admitted to the hospital with a history of anorexia, weight loss and vomiting of 3 years' duration. A total gastrectomy with enteroenterostomy was performed on May 28, 1936. The pathological diagnosis of Dr. Tracy B. Mallory was adenocarcinoma without metastases in the adjacent lymph nodes or extension to the duodenum. One year later, when reoperation was necessary to establish a new enteroenterostomy, no evidence of cancer was discovered. Since the second operation, the patient's condition has been excellent, and she has carried on her work as a housekeeper without difficulty. Postoperatively, she received liver and iron prophylactically until July 15, 1946.

CASE 2. R. V., a 49-year-old Italian, was admitted to the hospital with a history of increasing pallor, weakness and anorexia of indefinite duration. For 2 weeks he had felt a mass in the abdomen. On August 20, 1941, a total gastrectomy, splenectomy, subtotal pancreatectomy and enteroenterostomy were performed. The pathological diagnosis of Dr. Mallory was adenocarcinoma. The patient made a moderately good recovery and slowly regained weight. Three years after operation the red-cell count was 4,400,000, with a hemoglobin of 80 per cent. At the end of 5 years, when he was first seen at this hospital, he had lost 10 pounds in weight, although he was still feeling moderately well. Blood studies revealed macrocytosis and hyperchromia (Table 1).

CASE 3. W. M., a 41-year-old man, was admitted to the hospital with a history of intermittent indigestion of 8 years' and epigastric pain, poor appetite and weight loss of 4 months' duration. X-ray examination revealed an ulcer high on the lesser curvature. Since cancer was suspected, total gastrectomy was carried out on August 8, 1943. The pathological diagnosis of Doctor Benjamin Castleman was acute and chronic gastritis with multiple gastric ulcers. The patient was discharged on the 13th postoperative day and remained well for 2 years. He then began to lose his appetite and to feel weak. Pallor was noted, and examination of the blood showed a macrocytic, hyperchromic anemia, which responded to injections of liver extract‖ (Table 1). No liver was given after July 9, 1946, but no anemia had developed as of March 17, 1947.

GASTROINTESTINAL FUNCTION

When the first patient who survived total gastrectomy was studied fifty years ago, it was noted with surprise that she regained her appetite,[25–26] and since then, others have observed that the stomach is not necessary for this sensation.[27–30] All our patients have a normal desire for food and develop hunger. The patient in Case 1 takes three meals a day and only occasionally eats between meals; the meals are of nearly normal size. Another patient (Case 2) has persisted in taking in-between feedings and a bedtime snack. The third patient has to eat irregularly because of his work, but four times a day, on the average, he takes meals about two thirds the size of those consumed before his illness. All 3 patients are on an unrestricted, mixed diet, but take care that the food is well cut and well chewed. Occasionally, they experience borborygmi and mild upper abdominal cramps after eating, and too rapid eating may produce an epigastric sensation of fullness. None of these patients have dysphagia or symptoms suggesting the "dumping syndrome." The weight, although it increased after the operation, has never regained the levels existing before illness.

Fluoroscopic and radiologic examination revealed a normal esophagus and a patent, well functioning esophagojejunal anastomosis. In Cases 1 and 2 the jejunal segment at the anastomosis was dilated, with no mucosal markings except a few thickened valvulae conniventes. The barium meal tended to puddle in these jejunal reservoirs (Fig. 1). In Case 3 jejunal dilatation was not seen. The motor pattern of the lower jejunum and ileum of all 3 patients mani-

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¶These 3 cases were made available through the courtesy of Dr. Reginald H. Smithwick,[1] who has described the operative details elsewhere.

‖These observations were made by Dr. James A. Halsted at the Massachusetts General Hospital.

fested minimal to moderate abnormalities of the type seen in the "deficiency pattern" of Golden.[21] Films taken five hours after the ingestion of the barium meal demonstrated the opaque medium in the ileum and ascending colon in Case 1. In Case 3, however, the meal was still confined to the small bowel, and in Case 2 only a few jejunal loops were seen, most of the meal still being retained in the jejunal reservoir. The twenty-four-hour films showed a normal distribution of the barium meal in all 3 cases.

Kymographic records of small-intestine motility were obtained by a method previously described.[22]

tain chyme for considerable periods, are prone to develop after total gastrectomy, presumably in an attempt to compensate for the absent reservoir function of the stomach. The findings in Case 3, however, suggest that this jejunal dilatation is neither invariable nor apparently necessary.

Studies of fat absorption were carried out as follows. The patients, who were on a routine hospital diet, ingested between 40 and 60 gm. of fat a day. An accurate and constant fat intake was not feasible because the subjects, who felt perfectly healthy, did not wish to stay in the hospital for more than a week, and many tests were carried out during that time.

TABLE 1. *Blood Findings in Patients Who Lived Three or More Years after Total Gastrectomy.*

SURGEON	DATE OF OPERATION	AGE	SEX	DIAGNOSIS	ONSET OF ANEMIA AFTER OPERATION	RED-CELL COUNT	HEMOGLOBIN	COLOR INDEX
Patients developing macrocytic blood picture:		yr.			yr.	x10⁶		
Dennig[3]	1918	41	M	Ulcer	8	1.4	35%	1.25
Kelly[3]	1939	45	M	Carcinoma	4	2.2	55%	1.25
Marshall[4]	1939	40	F	Lymphoblastoma	7	1.6	7.7 gm.	—
Mayo (Hartman[5, 6])	1917	58	M	Carcinoma	2	—	48–53%	1.2–1.6
Mayo (Weir[7])	1937	37	M	Ulcer	8	3.22	13.2 gm.	—
Meyer[8]	1933	33	M	Gastritis (nonspecific)	5	1.6	55%	—
Poole and Foster[9, 10]	1926	36	F	Gastritis (? syphilitic)	3	0.5	20%	—
Ransom[11]	1940		F	Carcinoma	4,5	1.6	5.7 gm.	—
Ransom (Bethell[12])	1941	56	M	Ulcer	5	3.6	14.9 gm.	—
Smithwick[1]	1941	49	M	Carcinoma	5	2.9	11.0 gm.	—
Smithwick[1]	1943	41	M	Ulcer	2	2.06	7.8 gm.	1.2
Zollinger[13]	1938	66	M	Carcinoma	8 (6 mo. after stopping liver)	1.28	5.1 gm.	—
Patients developing anemia of doubtful nature:								
Lobenhoffer (Breitenbach[14])	1922	41	M	Ulcer	6	1.8	39%	1.08
Meyer (Stahnke[15] and Koch[17])	1931	40	F	Carcinoma	8	2.0–6.0	45–83%	>1
Morrison[18, 19]	1938	68	M	Carcinoma		—	—	—
Moynihan[16]	1907	43	M	Carcinoma	3	—	—	—
Streicher[21, 22]	1932	45	F	Carcinoma	3	—	—	—

The motility records corresponded well with the roentgenologic findings (Fig. 2). The jejunum near the anastomosis in Cases 1 and 2 exhibited atony and an absent wave pattern. Only after motility had been stimulated by the ingestion of an eggnog did motor waves appear. The lower jejunum in Cases 1 and 2 and the entire jejunum in Case 3 yielded essentially normal motility records. Both radiologic and motility studies of the intestine indicate that large jejunal reservoirs, which may re-

The stools were collected for three days, acidified and dried in toto over a steam bath. The dried feces were then finely powdered, and a 10-gm. portion was extracted in a Soxhlet apparatus with petroleum ether. With such a method, some volatile lipids may be lost, but difficulties encountered with wet methods, such as small, nonrepresentative aliquots and difficult fat extraction, are avoided.

When the intake of fat is small, the absolute daily fecal fat excretion is more significant than the pro-

portion of fat output to fat intake, or the percentage of fat in the dried stool.[33] A normal person ingesting no more than 60 gm. of fat a day usually excretes less than 5 gm. and invariably less than 10 gm. in the stools. According to these criteria, the fecal fat excretion of 2 patients was in the high normal range (Table 2), whereas only Case 2 exhibited a frankly abnormal output of fat in the stools. This patient, it will be recalled, had undergone a partial pancreatectomy.

Table 2 also lists the findings of others who have studied fat absorption after total gastrectomy.[14, 25, 26, 34–48] The wide divergence of results is striking but can partly be attributed to differences in fat intake and in subject material. In some cases, for example, the patients were studied early in the postoperative period before readjustment of gastrointestinal function was complete; in others, the patients subsequently died of recurrent carcinoma with the result that the effects of total gastrectomy and of the recurrent disease are hard to separate. The report of Heilmann,[44] often credited with describing a fat loss of 52 to 74 per cent, contains equivocal data, which others have also found difficult to interpret.[34] Nevertheless, even after exclusion of cases that are theoretically subject to criticism, one is confronted, on the one hand, by a patient who a year after operation lost 23 gm. of fat[42] and, on the other, by a patient who four years after operation excreted less fat than many a normal person does.[37]

Although an occasional case with frank steatorrhea may be encountered, the data presented in the literature and our own studies indicate that fat absorption is only mildly impaired in patients who have survived total gastrectomy for two or more years. If the fat intake is low, the absolute amount of fat lost is not large, but on high-fat diets, a considerable excretion of fecal fat may take place. The careful studies of Wollaeger et al.[48] indicate that fat absorption is similarly affected after partial gastrectomy.

The absorption of fat-like substances was further studied by means of the vitamin A tolerance test, 300,000 units being given by mouth. The results indicate that the blood in Cases 1 and 3 achieved a normal increase of vitamin A but that the tolerance curve in Case 2 was quite flat (Fig. 3). A remarkable

TABLE 1 (*Continued*).

Mean Corpuscular Volume	Mean Corpuscular Hemoglobin	Red-Cell Diameter	Hematocrit	White-Cell Count	Remarks
cu. microns	*microgm.*	*microns*	%	$\times 10^3$	
—	—	—	—	4.0	Blood smear showed nucleated red cells; spinal-cord involvement observed; patient responded to liver therapy but contracted pneumonia and died 9 yr. postoperatively.
—	—	—	—	—	Blood smear showed macrocytosis and hyperchromia; patient responded to liver and iron therapy, and was living 8 yr. postoperatively.
136	—	—	21.8	4.7	Blood smear showed nucleated red cells; spinal-cord changes observed; no response to intravenous folic acid, but patient responded to liver therapy and was living 8 yr. postoperatively.
—	—	—	—	—	Patient had chronic diarrhea; patient died nearly 4 yr. postoperatively.
—	—	8.1	—	—	Blood smear showed moderate macrocytosis; no megaloblastic changes in bone marrow; liver response not reported; patient living 9 yr. postoperatively.
—	—	—	—	8.45	Reticulocyte count, 1.2 per cent; blood smear and bone marrow typical of pernicious anemia; no response to extrinsic factor and vitamin C; patient responded to liver therapy but died 6 yr. postoperatively.
—	—	—	—	1.15	Patient, who responded to liver therapy, was living 20 yr. postoperatively
106	—	—	17.0	2.45	Patient, who responded to liver therapy, was living 6.5 yr. postoperatively
122	—	—	44.0	7.65	Patient, who responded to oral folic acid therapy, was living 5 yr. postoperatively
118	37.9	—	34.2	6.87	No bone-marrow biopsy; slight response to prolonged folic acid therapy; patient living 5.5 yr. postoperatively.
—	—	—	—	5.0	Blood smear showed macrocytosis, anisocytosis and tailed cells; no bone-marrow biopsy; patient, who responded to liver therapy, living 3.5 yr. postoperatively.
115	40.9	—	14.7	2.2	Blood smear showed macrocytosis; bone marrow showed megaloblastic picture: patient, who responded to oral folic acid therapy, living 9 yr. postoperatively.
—	—	—	—	4.2	Blood smear similar to that in pernicious anemia, but no nucleated red cells seen; 1 liver therapy; patient probably that referred to by Ducuing[48] as having died of pernicious anemia 11 yr. postoperatively.
—	—	—	—	—	No response to liver until administration of iron intravenously; patient living 8 yr. postoperatively.
—	—	—	—	—	Blood picture stated to reveal "macrocytic anemia"; patient responded to liver therapy but died of metastasis 3.5 yr. postoperatively.
—	—	—	—	—	Blood picture stated to reveal "profound anemia" (no blood count given); patient improved but relapsed, dying 3.7 yr. postoperatively; no metastasis found at autopsy (incomplete study).
—	—	—	—	—	"Macrocytic anemia" stated to have developed while patient was on prophylactic liver therapy; patient died of metastasis 4 yr. postoperatively.

feature is the delayed absorption of the vitamin that appears to take place in all these cases. When vitamin A is injected into the jejunum of a normal person, the blood level is sharply elevated two hours after the injection.[46] The two-hour to three-hour levels of vitamin A in the gastrectomy cases, contrary to all expectations, were lower than corresponding levels obtained in normal persons taking the test dose by mouth. Two possible explanations are offered for the delayed absorption of vitamin A: the test dose, which is small in volume, is retained in the jejunal reservoirs until the patient is allowed to eat and drink (after the three-hour sample); and pancreatic and biliary secretions, which facilitate the absorption of vitamin A[46] and which enter the bowel considerably above the esophagojejunal anastomosis, mix with the test dose only after considerable delay.

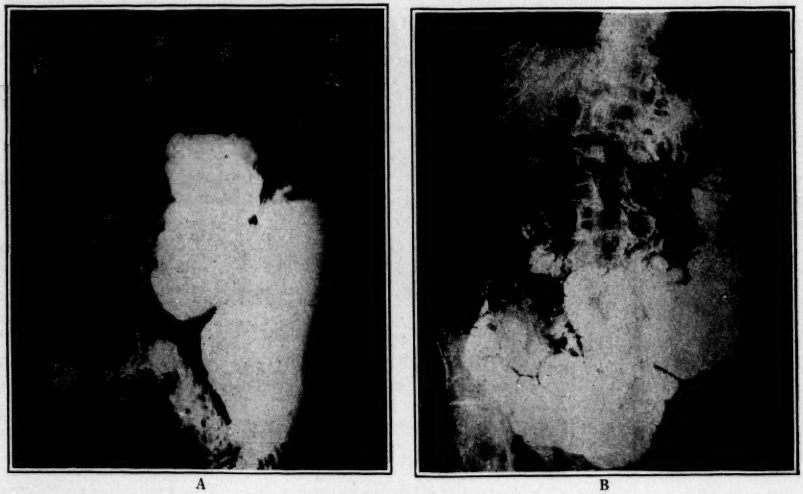
Judging from the prothrombin times (Table 3), the absorption of fat-soluble vitamin K is adequate. The normal serum levels of calcium and phosphorus also indicate that at least some vitamin D is being absorbed. Roentgenograms of the spine and pelvis revealed normal bone studies in 2 cases. In Case 1 considerable osteoporosis was noted, but no more than was evident before operation.

A normal person on an average diet excretes between 1 and 2 gm. of nitrogen a day.[49] As Table 2 indicates, our cases and those reported in the literature show little variation from normal. The largest nitrogen loss, 4.8 gm., was reported by Bull,[34] whose patient was studied three and a half months after operation and was given a high-fat diet.

It has been postulated that the secretion of pancreatic enzymes is greatly reduced after removal of the stomach.[47] Deficient pancreatic secretion may result either because the vagi are sectioned at operation or because the duodenal mucosa does not elaborate secretin normally if acid chyme fails to enter the duodenum. Pancreatic-enzyme studies in our cases, however, yielded essentially normal figures except in Case 2, in which a partial pancreatectomy had been performed (Table 4).

Standard methods for collecting pancreatic secretions from the duodenum could not be carried out because of the operative procedure. Furthermore, it was considered desirable to determine the response of the pancreas to food intake after total gastrectomy rather than the response to Mecholyl or secretin. Accordingly, an eggnog of standard composition was given to each patient after a collecting tube had been placed in the jejunum under fluoroscopic control. Half an hour later, constant suction was applied, and intestinal chyme collected in an iced container for one hour. The aspirated material was relatively free of eggnog.

None of the patients had symptoms referable to biliary-tract disease. An oral Graham–Cole test in



A B

FIGURE 1. *Dilatation of Jejunal Segment at Esophagojejunal Anastomosis.*
A *demonstrates puddling of the barium meal in Case 1, and* B *that in Case 2.*

Case 1 did not demonstrate any gall-bladder shadow. The other patients received the dye intravenously, and a normal filling of the viscus resulted in both reasons: absorption from the dilated small bowel is often subnormal, and dilatation of jejunal segments not only may delay fat absorption by the pooling

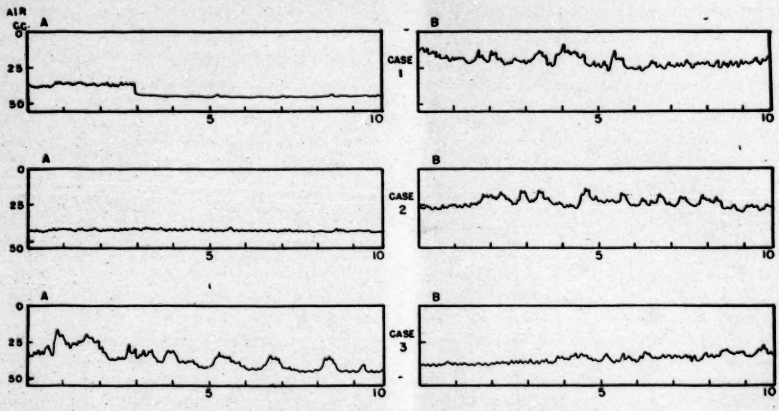


FIGURE 2. *Balloon Kymographic Tracings of Jejunal Motility in Cases 1, 2 and 3.*
Tracing A was taken just below the esophageal anastomosis; tracing B refers to the lower jejunum. The vertical calibrations refer to air in the balloon, and the horizontal markings to time in minutes.

cases; administration of a fat meal produced normal emptying of the gall bladder.

Glucose-tolerance curves obtained after the 3 subjects had ingested 50 gm. of glucose in 200 cc. of water are presented in Figure 4. The early hyperglycemia that occurs in patients with extensive gastrectomies because a large quantity of hypertonic glucose solution rapidly enters the small intestine is well demonstrated and apparently is not affected by the presence of jejunal reservoirs. After the initial rise in blood sugar, a hypoglycemia attributed to excessively stimulated glucose removal mechanisms has been found in some of these patients,[47, 83] but such a response was not observed in our subjects. As a matter of fact, Case 2 exhibited a continuing hyperglycemia of the diabetic type, possibly related to the partial pancreatectomy that had been performed.

Significant impairment of fat absorption was demonstrated only in Case 2, but the deficiency of pancreatic enzymes in this patient suggests that the partial pancreatectomy was at least a contributing factor in the pathogenesis of the steatorrhea. In general, our studies indicated that such loss of fecal fat as may occur after total gastrectomy is not due to deranged function of the biliary tract or pancreas. By analogy to the delayed absorption of vitamin A, however, it is possible that the absorption of fats is impaired by mechanical disorders, for the following of ingested food but also may decrease fat absorption by curtailing the length of normally functioning small intestine; and if jejunal pooling is minimal or

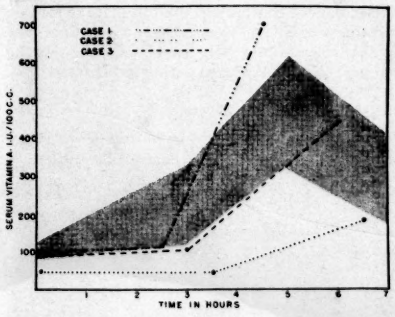


FIGURE 3. *Vitamin A Tolerance Curves following Oral Ingestion of 300,000 International Units.*
The shaded area represents the normal range.

is counteracted by the ingestion of a large meal, fats may be propelled for some distance down the intestine before pancreatic and biliary secretions

"catch up" with the meal. Under such conditions, fat absorption may be impaired because a relatively short stretch of small bowel is exposed to properly digested fats. In this connection, the pancreatic-function studies indicated that the jejunal reservoirs were practically free of eggnog half an hour after its hematologic findings in the other case were normal, but the patient had received liver prophylactically after operation. This incidence of macrocytic anemia prompted a renewed inquiry into the much debated question whether total gastrectomy predisposes toward a pernicious-anemia type of blood

TABLE 2. *Excretion of Fat and Nitrogen in Stools.*

SOURCE OF DATA	YEAR OF REPORT	DIAGNOSIS	AGE OF PATIENT	SEX	INTERVAL BETWEEN OPERATION AND STUDY	INTAKE			FAT LOSS IN STOOL			PROTEIN LOST AS NITROGEN
						CARBOHYDRATE	PROTEIN	FAT	PER DAY	PERCENTAGE OF INTAKE	PERCENTAGE DRY WEIGHT OF FECES	PER DAY
			yr.			gm.	gm.	gm.	gm.			gm.
Present report (Case 1)	1947	Carcinoma	58	F	10 yr.	—	—	40–60	8.0	—	37.4	0.9
Present report (Case 2)	1947	Carcinoma	49	M	5 yr.	—	—	40–60	14.5	—	35.0	2.2
Present report (Case 3)	1947	Ulcer	41	M	3 yr.	—	—	40–60	7.8	—	19.1	2.6
Breitenbach[34]	1929	Ulcer	41	M	6.5 yr.	165	138	135	8.1	6.0	—	0.9
Breitenbach[34]	1929	Carcinoma	51	F	5 wk.	126	91	116	8.2	7.1	—	0.6
Breitenbach[34]	1929	Carcinoma	—	—	3 mo.	—*	—*	—*	—	7.0	—	—
Bull and Stang[35]	1934	Carcinoma	40	M	14 wk.	243	95	137	41.3	30.1	—	4.8
Bürger and Konjetzny[35]	1929	Carcinoma	49	F	3 wk.	96	34	86	10.2	11.9	—	0.4
Butler[36]	1927	Ulcer	42	M	5 mo.	—†	—†	—†	—	—	38.0	—
Farris et al.[37]	1943	Neuro-fibroma	40	F	4 yr.	245	67	89	1.5	1.7	7.3	0.8
Flint[38]	1928	Carcinoma	44	M	5 mo.	—‡	—‡	—‡	—	—	40.7	—
Hofmann[39]	1898	Carcinoma	56	F	5.5 mo.	185	93	84	4.6	5.5	—	—
Wróblewski[39]	1898	Carcinoma	56	F	1 mo.	—	—	—	13.3	—	37.6	—
Kobelt[39]	1922	Carcinoma	45	F	1 mo.	—	72	33	7.6	—	—	2.0
Longmire[40, 41]	1947	Carcinoma	57	M	23 mo.	—	—	77	30.8	40.2	41.3	—
Longmire[40, 41]	1947	Carcinoma	53	M	29 mo.	—	—	77	23.1	30.2	31.1	—
Longmire[40, 41]	1947	Carcinoma	58	F	22 mo.	—	—	77	7.2	9.4	25.2	—
Longmire[40, 41]	1947	Carcinoma	62	M	24 mo.	—	—	77	7.8	10.2	18.5	—
Rekers et al.[42]	1943	Carcinoma	42	F	1.1 yr.	—	25	50	12.0	24.0	—	1.0
Rekers et al.[42]	1943	Carcinoma	55	M	4 mo.	—	77	70	11.0	16.0	—	1.3
Rekers et al.[42]	1943	Carcinoma	59	M	Over 1 yr.	—	62	40	23.0	57.0	—	2.2
Troell et al.[43]	1927	Carcinoma	47	M	5 wk.	304	118	182	34.4	18.9	—	3.1

*Not stated — probably same amount as that in second Breitenbach case.
†Stated as "full diet."
‡Stated as "ordinary diet."

ingestion, but that at that time considerable quantities of relatively pure bile and pancreatic juice had collected in the dilated bowel loops.

Speculation concerning the ultimate effects of vagotomy on biliary, pancreatic and intestinal function has recently been rife. Since complete vagotomy is almost always performed during total gastrectomy, it is of interest that our patients did not manifest the dire results that have been predicted as sequelae to section of the vagus nerves.

MACROCYTIC ANEMIA

As shown in Table 1, 2 patients developed a macrocytic, hyperchromic anemia two and five years, respectively, after total gastrectomy. The picture. On theoretical grounds, it should, for Castle[54, 55] has shown that in man, as opposed to some animals,[56] the stomach is the only source of the intrinsic antianemic factor. Clinical experience, however, suggests that total gastrectomy in man is not followed by a macrocytic hyperchromic anemia, although an iron-deficiency anemia occasionally occurs. Thus, Pack and McNeer[57] state that a macrocytic anemia is rare after total gastrectomy, and that when it is found, it is seldom hyperchromic and usually does not respond to adequate liver therapy.

TABLE 3. *Pertinent Data in 3 Cases after Total Gastrectomy.*

CASE NO.	SERUM CALCIUM	SERUM PHOSPHORUS	SERUM CHOLESTEROL	TOTAL PROTEIN	SERUM ALBUMIN	SERUM GLOBULIN	ALBUMIN-GLOBULIN RATIO	PROTHROMBIN TIME		BROMSULFALEIN REMOVAL CONSTANT[58]
								PATIENT	CONTROL	
	mg./100 cc.	mg./100 cc.	mg./100 cc.	gm./100 cc.	gm./100 cc.	gm./100 cc.		sec.	sec.	%
1	9.94	3.62	165	6.49	4.13	2.36	1.75 : 1.0	23.7	23.0	11.45
2	8.74	3.52	177	5.85	3.22	2.63	1.23 : 1.0	22.2	22.5	7.80
3	10.20	3.34	173	6.60	3.98	2.62	1.52 : 1.0	23.8	23.7	15.20

The blood findings in our patients suggested the hypothesis, which had already been advanced by others,[58] that patients with total gastrectomy de-

velop macrocytosis and hyperchromia provided they live long enough after the operation. For this reason, we have collected from the literature and by personal correspondence as many cases of three-year survival after total gastrectomy as possible, and have attempted to ascertain the incidence of macrocytic anemia in this group.[3–22, 27–30, 36, 39, 59–84] Some cases previously cited as three-year survivals died one year postoperatively of acute small-bowel obstruction. At autopsy no evidence was found of recurrence of carcinoma. This case has been omitted from Table 1, which is limited to three-year survivals.

The 29 patients who apparently did not develop a macrocytic anemia include 10 who definitely had not received prophylactic liver therapy. No definite

TABLE 4. *Enzyme Analysis of Jejunal Chyme.*

Case No.	Vol. in 1 hr.	Amylase*		Lipase†		Trypsin‡	
			total		total		total
	cc.	units/cc.	units in 1 hr.	units/cc.	units in 1 hr.	units/cc.	units in 1 hr.
1	80.0	11.0	880.0	61.2	4,896.0	200.0	16,000.0
2	107.0	2.2	235.4	16.1	1,723.0	3.1	331.7
3	48.5	10.3	499.5	49.2	2,386.2	200.0	9,700.0

*Determined by method of Lagerlöf.[85]
†Determined by method of Crandall and Cherry.[51]
‡Determined by method of Andersen and Early,[52] slightly modified.

after total gastrectomy are not included because removal of the stomach was not total. For similar reasons, or because of insufficient data, certain cases of alleged macrocytic anemia after total gastrectomy are excluded.[85–92]

After exclusion of patients definitely known to have received prophylactic treatment with liver, 46 information is available whether or not liver was given in the other 19 cases (Table 5).

In the 12 cases with macrocytosis and hyperchromia, a pathological diagnosis of ulcer or gastritis was made in half, whereas none of those with malignant lesions had any evidence of recurrence. Generally speaking, these patients had a satisfactory

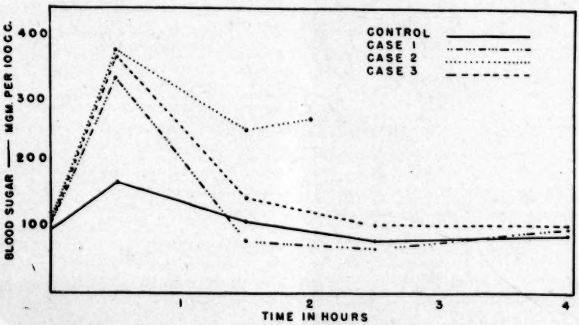


FIGURE 4. *Oral Glucose-Tolerance Curve following Administration of 50 gm. of Glucose Dissolved in 200 cc. of Water.*

cases remain. Of these, 12 appear to have had blood findings resembling those of pernicious anemia, and 5 others had anemias of doubtful nature.

Another case of macrocytosis and hyperchromia — red-cell count of 3,810,000, hemoglobin of 95 per cent (Sahli), mean red-cell diameter of 8.8 microns and nucleated red cells found on smear — is reported by Ungley.[93] This blood picture developed five months after total gastrectomy, but the patient surgical result, and it seems probable that their diet was adequate. It is noteworthy that 3 cases showed a definite reduction in the red-cell count, with an increase in the mean corpuscular volume, but relatively little decrease in hemoglobin. It is possible that this is the earlier stage of this type of anemia.

Macrocytic anemias seldom occurred less than two years after operation. This finding was also

noted in the studies of similar anemias occurring after less radical gastric resection.[94, 95] Why so long a time is required to develop this blood picture is unknown. Schwartz and Legere[96] recently reported that self-induced relapses in 54 patients who had have been administered indiscriminately, and special studies like reticulocyte counts and bone-marrow examinations have been few. Only if macrocytic anemias that follow total gastrectomy are carefully investigated by the methods used by Meyer et al.[5]

TABLE 5. *Patients Surviving Total Gastrectomy for Three or More Years without Developing a Macrocytic Anemia.*

SURGEON	DATE OF OPERATION	AGE	SEX	DIAGNOSIS	REMARKS
Patients not given liver therapy:		yr.			
Berg (Rosenthal–Abel[89])	1931	51	M	Carcinoma	Patient died 3 yr. after operation
Brigham[87]	1898	66	F	Carcinoma	Patient well 8 yr. after operation
Brun (Kobelt[88])	1916	45	F	Carcinoma	Patient died of chronic nephritis 4 yr. after operation
Butler (Hurst[89])	1926	42	M	Ulcer	Patient well 5 yr. after operation, with normal blood picture
Diaz (Milanés[90])	1941	54	M	Carcinoma	Patient well until sudden death from cardiac failure 4 yr. after operation
von Haberer[84]	1920	56	M	Ulcer	Patient died of tuberculosis 6 yr. after operation
von Herczel[85]	1901	42	F	Carcinoma	Patient well 5 yr. after operation
MacDonald[86]	1898	38	M	Carcinoma	Patient well 7 yr. after operation
Ransom (Farris et al.[97])	1938	40	F	Neuro-fibroma	Patient well 8½ yr. after operation
Wrede[87]	1919	36	M	Carcinoma	Patient well 4 yr. after operation
Definite information on liver therapy not available*:					
d'Allaines[83]	1941	44	M	Carcinoma	Patient well 3½ yr. after operation
Allen[93]	—	—	M	Carcinoma	Patient died 4½ yr. after operation
Joll[78]	1932	45	M	Carcinoma	Patient died 3 yr. after operation
Joll[78]	1938	42	F	Carcinoma	Patient died 3½ yr. after operation
Lahey Clinic operators (Smith[56])	1938	50	M	Carcinoma	Patient died 4¾ yr. after operation
	1940	64	M	Carcinoma	Patient well 5½ yr. after operation
	1941	51	F	Lymphoma	Patient well 4¾ yr. after operation
	1941	60	F	Carcinoma	Patient failing 4 yr. after operation
	1941	62	F	Carcinoma	Patient died 3 yr. after operation
	1942	64	F	Carcinoma	Patient well 3¾ yr. after operation
	1942	51	M	Lympho-sarcoma	Patient well 3¾ yr. after operation
	1942	57	M	Carcinoma	Patient died 3½ yr. after operation
	1943	56	F	Chronic gastritis	Patient well 3 yr. after operation
Mayo Clinic operators (Waugh and Fahlund[79])	—	—	—	"Malignancy"	Patient alive over 3 yr. after operation
				"Malignancy"	Patient alive over 3 yr. after operation
				Benign tumor	Patient alive over 6 yr. after operation
Roeder[72, 74]	1932	50	M	Ulcer	Patient well until sudden death from cardiac failure 6 yr. after operation
Soo[75]	—	—	—	Carcinoma	Patient living 3 yr. after operation
Weese[76]	—	—	—	Carcinoma	Patient died 3½ yr. after operation
Patients given liver therapy prophylactically:					
Allen[92, 93]	1939	39	F	Carcinoma	Patient died 4¼ yr. after operation
Lahey Clinic operators (Ciute[77, 78])	1929	36	F	Carcinoma	Patient died 3¼ yr. after operation
Lahey Clinic operators (Smith[56])	1937	27	F	Leiomyo-sarcoma	Patient well 8½ yr. after operation
Morton[70, 80]	1939	48	F	Carcinoma	Patient well 8 yr. after operation
Morton[70, 80]	1940	38	M	Carcinoma	Patient well 7 yr. after operation
Ransom[11]	1938	52	M	Carcinoma	Patient had pernicious anemia preoperatively; well 8 yr. after operation.
Smithwick[1]	1936	58	F	Carcinoma	Patient well 10½ yr. after operation

*Most of the patients operated on at the Lahey Clinic probably received liver.[56]

been treated with liver occurred two to thirty-eight months after cessation of therapy for pernicious anemia. They stress the fact that relapse is a highly singular phenomenon that is unpredictable in any given case. This individual variation is also seen in the macrocytic anemias after total gastrectomy.

The evidence appears to support the statement that an anemia morphologically similar to Addisonian pernicious anemia will develop after total gastrectomy if the patient survives long enough. Whether the anemia is truly Addisonian, or whether it is another form of macrocytic anemia requires further study. In the past, most patients developing macrocytic anemia after total gastrectomy have been incompletely studied, for the effects of dietary deficiency have not been excluded, liver and iron can their relation to Addisonian pernicious anemia be clarified.

SURVIVAL

A review of the literature to determine the incidence of anemia in patients surviving total gastrectomy for more than three years uncovered so many inconsistencies and forgotten cases that a note on the period of survival following total gastrectomy seems indicated.

Until recently, the patient of Zikoff[97] was considered the longest survival after total gastrectomy for carcinoma, since Finney and Rienhoff[98] reported her alive four years and eight months after operation. Zikoff's article, however, is an early postoperative report, which does not contain any in-

formation concerning subsequent survival. Attention is directed to a much overlooked reference, the Hunterian lecture of 1906, by H. J. Paterson.[29] In this monograph, he quotes a personal communication from MacDonald, of San Francisco, to the effect that the patients of Brooks Brigham and of MacDonald were alive and well eight and seven years after their operations, which, incidentally, were the second and third successful total gastrectomies reported in the literature. One of the patients studied by us is alive and well ten and a half years postoperatively, whereas the patient described by Poole and Foster[9] is still alive and well 20 years after the complete removal of the stomach for a nonmalignant condition.[10] These 2 cases appear to represent the longest known survivals after total gastrectomy for malignant and nonmalignant tumors respectively.

Summary

Studies on 2 patients who had survived total gastrectomy ten and three years respectively and on 1 who had survived total gastrectomy, splenectomy and partial pancreatectomy five years revealed the clinical condition of the patients with total gastrectomy alone to be excellent. Considerable dilatation of the jejunum near the esophagojejunal anastomosis was demonstrated by roentgenologic and kymographic methods in 1 case. In both cases, pancreatic enzymes were normal, and fat absorption on a low-fat intake was not significantly impaired. Vitamin A tolerance curves showed an apparently delayed but otherwise normal absorption of the vitamin. Glucose-tolerance tests disclosed an early and marked, but transient, hyperglycemia.

The patient with total gastrectomy, splenectomy and partial pancreatectomy experienced difficulty in maintaining weight. Dilatation of the jejunum was present. Pancreatic enzymes were deficient, fat absorption impaired, and the vitamin A tolerance curve flat. The glucose-tolerance curve showed a hyperglycemia, which was sustained.

Blood studies demonstrated that 2 of the 3 patients developed a macrocytic, hyperchromic anemia two and five years respectively after operation. The other had received prophylactic liver treatment. A review of the literature revealed a high incidence of macrocytic, hyperchromic anemia in patients surviving total gastrectomy for three or more years.

References

1. Smithwick, R. H. Total gastrectomy: with particular reference to closed (aseptic) esophagojejunostomy. *New Eng. J. Med.* **237**: 39-48, 1947.
2. Dennig, H. Perniziöse Anämie nach Magenresektion. *München. med. Wchnschr.* **76**:633, 1929.
3. Kelly, C. C. Personal communication.
4. Marshall, S. F. Personal communication.
5. Hartman, H. R. Blood changes in gastrectomized patient simulating those in pernicious anemia. *Am. J. M. Sc.* **162**:201-206, 1921.
6. Hartman, H. R., and Eusterman, G. B. Anemia following operations on stomach. *Am. J. Digest. Dis. & Nutrition* **1**:829-834, 1935.
7. Weir, J. F. Total gastrectomy: report of patient surviving eight years. *S. Clin. North America* **26**:934-940, 1946.
8. Meyer, K. A., Schwartz, S. O., and Weissman, L. H. Pernicious anemia following total gastrectomy. *Arch. Surg.* **42**:18-24, 1941.
9. Poole, A. K., and Foster, L. C. Chronic syphilitic (?) gastritis with total gastrectomy and pernicious anemia. *J. A. M. A.* **96**:2187-2190, 1931.
10. Poole, A. K. Personal communication.
11. Ransom, H. K. Personal communication.
12. Bethell, F. H., et al. Metabolic function of pteroylglutamic acid and its hexaglutamyl conjugate. I. Hematologic and urinary excretion studies on patients with macrocytic anemia. *J. Lab. & Clin. Med.* **32**:3-22, 1947.
13. Zollinger, R. M., and Finch, C. Personal communication.
14. Breitenbach, G. Stoffwechselversuch nach totaler Magenresektion. *München. med. Wchnschr.* **76**:1920, 1929.
15. Ducuing, J., Soula C., and Fränkel, R. La gastrectomie totale chez l'homme. *J. de chir.* **44**:175-210, 1934.
16. Stahnke, E. N. Über totale Magenresektionen. *Zentralbl. f. Chir.* **60**:865-870, 1933.
17. Koch, H. Über unsere Erfahrungen in der Dauerbehandlung der perniziösen Anämie. *Deutsche med. Wchnschr.* **65**:1232-1237, 1939.
18. Morrison, W. B. Curability of cancer of stomach. *Ohio State M. J.* **37**:453-456, 1941.
19. *Idem.* Follow-up cited by Pack and McNeer.[37]
20. Moynihan, B. G. Case of complete gastrectomy. *Lancet* **2**:430 1911.
21. Streicher, M. H. Total gastrectomy (esophago-jejunostomy): unusual case. *Illinois M. J.* **65**:520, 1934.
22. *Idem.* Personal communication.
23. Schlatter, C. Unique case of complete removal of stomach: successful oesophago-enterotomy: recovery. *M. Rec.* **52**:909-914, 1897.
24. *Idem.* Oesophago-enterostomy after total extirpation of stomach. *Lancet* **1**:141-146, 1898.
25. Wróblewski, A. Eine chemische Notiz zur Schlatter'schen totalen Magenexstirpation. *Zentralbl. f. Physiol.* **11**:665-668, 1898.
26. Hofmann, A. Stoffwechseluntersuchungen nach totaler Magenresection. *München. med. Wchnschr.* **45**:560-564, 1898.
27. Brigham, C. B. Case of removal of entire stomach for carcinoma: successful esophago-duodenostomy: recovery. *Boston M. & S. J.* **138**:413, 1898.
28. *Idem.* After-history in case of successful total extirpation of stomach. *Philadelphia M. J.* **5**:247-249, 1900.
29. Paterson, H. J. *Gastric Surgery.* 181 pp. New York: William Wood & Co., 1906.
30. *Idem.* Gastric surgery. Lecture III. *Lancet* **1**:574-581, 1906.
31. Golden, R. *Radiologic Examination of the Small Intestine.* 239 pp. Philadelphia: J. B. Lippincott Co., 1945.
32. Ingelfinger, F. J., and Abbott, W. O. Intubation studies of human small intestine. XX. Diagnostic significance of motor disturbances. *Am. J. Digest. Dis.* **7**:468-474, 1940.
33. Wollaeger, E. E., Comfort, M. W., Weir, J. F., and Osterberg, A. E. Total solids, fat and nitrogen in feces. I. Study of normal persons and of patients with duodenal ulcer on test diet containing large amounts of fat. *Gastroenterology* **6**:83-92, 1946.
34. Bull, P., and Stang, J. Total gastrectomy for cancer with after-examinations of absorptive capacity of intestine. *Acta. chir. Scandinav.* **75**:319-328, 1934.
35. Bürger, M., and Konjetzny, G. E. Über die Nahrungsausnutzung nach Totalexstirpation des Magens. *Zentralbl. f. Chir.* **56**:1154-1158, 1929.
36. Butler, H. B. Case of complete gastrectomy for chronic ulcer, with observations on effect of loss of stomach on physiology of digestion in man. *Brit. J. Surg.* **15**:316-324, 1927.
37. Farris, J. M., Ransom, H. K., and Coller, F. A. Total gastrectomy: effects upon nutrition and hematopoiesis. *Surgery* **13**:823-833, 1943.
38. Flint, E. R. Case of complete gastrectomy for carcinoma of stomach. *Brit. M. J.* **2**:979, 1928.
39. Kobelt, H. Beitrag zur Totalexstirpation des Magens. 43 pp. Zurich: L. Hofer, 1922.
40. Longmire, W. P. Total gastrectomy for carcinoma of stomach. *Surg., Gynec. & Obst.* **84**:21-30; 1947.
41. *Idem.* Unpublished data.
42. Rekers, P. E., Pack, G. T., and Rhoads, C. P. Metabolic studies in patients with cancer of gastrointestinal tract. VI. Disorders in alimentary digestion and absorption in patients who have undergone total gastrectomy for carcinoma of stomach. *Surgery* **14**: 197-215, 1943.
43. Troell, A., Losell, G., and Karlmark, E. Fall von totaler Gastrektomie wegen Kanker. *Mitt. a.d. Grenzgeb. d. Med. u. Chir.* **40**: 542-549, 1927.
44. Heilmann, P. Stoffwechseluntersuchungen nach totaler Magenresektion. *München. med. Wchnschr.* **72**:178-182, 1925.
45. Wollaeger, E. E., Comfort, M. W., Weir, J. F., and Osterberg, A. E. Total solids, fat and nitrogen in feces. II. Study of persons who had undergone partial gastrectomy with anastomosis of entire cut end of stomach and jejunum (Polya anastomosis). *Gastroenterology* **6**:93-104, 1946.
46. Ingelfinger, F. J., Moss, R. E., and Helm, J. D., Jr. Effect of atropine upon absorption of vitamin A. *J. Clin. Investigation* **22**: 699-705, 1943.
47. Ingelfinger, F. J. Late effects of total and subtotal gastrectomy. *New Eng. J. Med.* **231**:321-327, 1944.
48. *Idem.* Hepatic function with respect to bromsulphalein removal. *Bull. New Eng. M. Center* **9**:25-29, 1947.
49. Peters, J. P., and VanSlyke, D. D. *Quantitative Clinical Chemistry.* Second edition. Vol. I. 1041 pp. Baltimore: Williams & Wilkins Co., 1946.

50. Lagerlöf, H. O. *Pancreatic Function and Pancreatic Disease Studied by Means of Secretin.* 289 pp. New York: Macmillan Co., 1942.
51. Crandall, L. A., Jr., and Cherry, I. S. Studies on specificity and behavior of blood and tissue lipases. *Proc. Soc. Exper. Biol. & Med.* **28**:570-572, 1931.
52. Andersen, D. H., and Early, M. V. Method of assaying trypsin suitable for routine use in diagnosis of congenital pancreatic deficiency. *Am. J. Dis. Child.* **63**:891-893, 1942.
53. Evensen, O. K. Alimentary hypoglycemia after stomach operations and influence of gastric emptying on glucose tolerance curve. *Acta med. Scandinav.* (Supp. 126) 1-188, 1941.
54. Castle, W. B. Observations on etiologic relationship of achylia gastrica to pernicious anemia. I. Effect of administration to patients with pernicious anemia of contents of normal human stomach recovered after ingestion of beef muscle. *Am. J. M. Sc.* **178**:748-764, 1929.
55. Fox, H. J., and Castle, W. B. Observations on etiologic relationship of achylia gastrica to pernicious anemia. IX. Difference in site of secretion of intrinsic factor in hog and human stomach. *Am. J. M. Sc.* **203**:18-28, 1942.
56. Meulengracht, E. Histologic investigations into pyloric gland organ in pernicious anemia. *Am. J. M. Sc.* **197**:201-214, 1939.
57. Pack, G. T., and McNeer, G. Total gastrectomy for cancer: collective review of literature and original report of twenty cases. *Internat. Abstr. Surg.* **77**:265-299, 1943.
58. Bethell, F. H., Sturgis, C. C., Rundles, R. W., and Meyers, M. C. Blood: review of recent literature. *Arch. Int. Med.* **76**:239-254, 1945.
59. Rosenthal, N., and Abel, H. A. Blood changes following partial or total gastrectomy. *Tr. Am. Gastro-Enterol. A.* **36**:215-225, 1933.
60. *Idem.* Follow-up cited by Pack and McNeer.[57]
61. Butler, H. B. Follow-up cited by Hurst, A. F. Achlorhydria and achylia gastrica, and their connexion with Addison's anaemia — subacute combined degeneration syndrome and simple (non addisonian) achlorhydric anaemia. *Quart. J. Med.* **1**:157-177, 1932.
62. Milanés, F., Vega, T., Morales, E., Rodriguez, A., and Rodriguez Diaz, A. Total gastrectomy: clinical and physiopathological study. *Gastroenterology* **3**:380-387, 1944.
63. Milanés, F. Personal communication.
64. von Haberer, H. Ergebnisse nach weitgehender Resektion bzw. Totalexstirpation des Magens bei Karzinom und Ulkus. *Deutsche med. Wchnschr.* **56**:562, 1930.
65. von Herczel, E. Beitrag zur totalen Exstirpation des carcinomatösen Magens. *Beitr. z. klin. Chir.* **34**:336-350, 1902. Cited by Paterson.[35]
66. MacDonald, G. C. Total removal of stomach for carcinoma of pylorus: recovery. *J. A. M. A.* **31**:538-540, 1898.
67. Wrede. Totale Magenresektion. *Med. Klin.* **15**:1298, 1919.
68. Allen, A. W. Total gastrectomy for carcinoma of stomach. *Am. J. Surg.* **40**:35-41, 1938.
69. Allen, A. W., and Welch, C. Personal communication.
70. Joll, C. A., and Adler, D. I. Long survival after total gastrectomy: brief review, with report of two cases. *Brit. M. J.* **2**:632-635, 1942.
71. Lahey, F. H., and Marshall, S. F. Indications for, and experiences with, total gastrectomy based upon 75 cases of total gastrectomy. *Ann. Surg.* **119**:300-320, 1944.
72. Waugh, J. M., and Fahlund, G. T. R. Total gastrectomy. *S. Clin. North America* **25**:903-917, 1945.
73. Roeder, C. A. Total gastrectomy. *Ann. Surg.* **98**:221-231, 1933.
74. *Idem.* Follow-up reported by Saint, J. H. Total gastrectomy for carcinoma: report of successful case. *West. J. Surg.* **51**:10-16, 1943.
75. Seo. Cited by Goto, S. Erfahrungen über die totale Extirpation des Magens. *Arch. f. klin. Chir.* **197**:385-394, 1939.
76. Weese, K. Ergebnisse der Magenkrebsbehandlung bei 883 Fällen in Zeitabschnitt 1921-1932. *Arch. f. klin. Chir.* **198**:202-242, 1940. Cited by Pack and McNeer.[57]
77. Clute, H. M., and Mason, R. L. Total gastrectomy for cancer of stomach: case report. *New Eng. J. Med.* **203**:909-913, 1930.
78. Clute, H. M. Postoperative course following total gastrectomy. *S. Clin. North America* **14**:1039-1048, 1934.
79. Morton, C. B., II. Total gastrectomy: indications for operation with report of 4 cases. *Arch. Surg.* **44**:72-80, 1942.
80. Morton, C. B. Personal communication.
81. Longmire, W. P., Paulson, M., and Harvey, J. C. Personal communication.
82. d'Allaines, F. deG. À propos de 18 cas de gastrectomie totale. *Arch. d. mal. de l'app. digestif* **34**:62-75, 1945.
83. Smith, F. H. Total gastrectomy: report of 89 cases. *Surg., Gynec. & Obst.* **84**:402-408, 1947.
84. Smith, F. H. Personal communication.
85. Gallet, A. Ablation totale de l'estomac et du côlon transverse; resection d'une portion de la tête du pancréas; guérison. *Bull. Soc. roy. d. sc. méd. et nat. de Bruxelles* **53**:52-58, 1900.
86. Ellis, A. Discussion on aetiology and treatment of subacute combined degeneration of spinal cord. *Proc. Roy. Soc. Med.* **18** (Sect. Neurol.): 21-27, 1925.
87. Cohn, M. Röntgenuntersuchung einer Frau, welcher der Magen und beide Nervi vagi reseziert worden sind. *Berl. klin. Wchnschr.* **50**:1393-1395, 1913.
88. Fasiani, G. M., and Chiatellino, A. Syndromes anémiques chez les opérés de l'estomac. *Presse méd.* **42**:2080-2084, 1934.
89. Treupel. Cited by Henschen, C. Über das Spätbludbild der Magenresezierten im Zusammenhang mit der Frage des Vorkommens von Resektionsanämien und deren Prophylaxe. *Arch. f. klin. Chir.* **162**:621-653, 1930.
90. Hurst, A. F. Addison's (pernicious) anemia and subacute combined degeneration of spinal cord. *Brit. M. J.* **1**:93-100, 1924.
91. Hochrein, M. Über Anämien nach Magenresektion. *München. med. Wchnschr.* **76**:1327, 1929.
92. Dollinger. Totale Magenexstirpation. *Ungar. med. Presse* **8**:155, 1902. Cited by Finney and Rienhoff.[93]
93. Ungley, C. C. Pernicious anemia following gastrectomy and splenectomy. *Lancet* **2**:1426, 1932.
94. Rowlands, R. A., and Levy Simpson, S. Addisonian anaemia following gastrectomy and gastro-jejunostomy. *Lancet* **2**:1202-1209, 1932.
95. Goldhamer, S. M. Pernicious anaemia syndrome in gastrectomized patients. *Surg., Gynec. & Obst.* **57**:257-260, 1933.
96. Schwartz, S. O., and Legere, H. Relapses in pernicious anemia. *J. A. M. A.* **124**:637-639, 1944.
97. Zikoff, V. M. Complete excision of stomach. *Novoye v. Med.* **5**:61-70, 1911.
98. Finney, J. M. T., and Rienhoff, W. F., Jr. Gastrectomy. *Arch. Surg.* **18**:140-162, 1929.

A REVIEW OF SOME RECENTLY DEFINED VIRUS DISEASES*

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DURING the decade 1920–1930, when I first began the study of infectious agents, it was more or less generally agreed that the era of etiologic discovery, if not definitely ended, was at least in its final stage. The efforts of bacteriologists in the future were to be directed to the more intensive study of the known pathogenic organisms — the number of which would not be materially increased— with a view to defining more precisely their metabolism, their chemistry, the immune reactions that they elicited and the means by which their attack might be prevented or withstood. However, we failed to visualize that rapid extension of its boundaries that was so soon to come! Since 1930 not only have the causative agents of such old and important diseases as yellow fever, influenza and mumps been determined but also the etiology of a large group of other infectious maladies, many of which had been clinically unrecognized, has been established. If the diseases of the lower animals that have been described during the same period are included the number of additions to this area of pathology becomes impressive indeed. To emphasize the fact that the age of etiologic discovery is far from ended, the following fairly complete list of diseases in man is given for which, within the period from 1940 to 1946, either conclusive or presumptive evidence of viral etiology has been presented: primary atypical pneumonia; Reimann's epidemic diarrhea; epidemic keratoconjunctivitis; Colorado tick fever; Russian spring-summer encephalitis; equine encephalomyelitis (Venezuelan strain); infectious jaundice; homologous serum jaundice; Dodd–Buddingh stomatitis and diarrhea of infants (final establishment of etiology requires confirmatory experiments); epidemic diarrhea of the newborn (final establishment of etiology requires confirmatory experiments); Fort Bragg fever or pretibial fever; West Nile fever (Africa); and Semliki forest fever (Africa). Indeed, after this list was prepared, a new virus disease was reported by a group of workers in Tennessee.[1] An outbreak of epidemic meningoencephalitis accompanied by vesicular pharyngitis affected over 200 persons, and inoculation of filtrates of nasopharyngeal washings from certain patients into the embryonated egg resulted in the isolation of what is tentatively described as a virus differing from any of the known agents.

It is my purpose to discuss mainly from the etiologic standpoint the first three diseases listed above. Of these primary atypical pneumonia and epidemic diarrhea have been of common occurrence in these regions. Epidemic conjunctivitis has been recognized in New York and the surrounding areas, although it seems first to have been clearly described on the Pacific Coast. As knowledge of it becomes more widely disseminated it is probable that more and more cases will be recognized.

PRIMARY ATYPICAL PNEUMONIA AND MINOR ACUTE UPPER RESPIRATORY ILLNESS

In a small number of patients with primary atypical pneumonia a fungous infection, the rickettsia of Q fever or the viruses of the psittacosis-ornithosis group have been shown to be involved.[2] But the determination of the nature of the agent responsible for the majority of cases has presented a baffling problem to investigators ever since this condition was recognized as a clinical entity in the years just preceding the war. At that time intensive efforts to reveal a virus in the blood, sputum and nasopharyngeal washings were made. These materials were obtained from patients studied clinically by Bock[3] and by Murray,[4] who were among the first to describe the disease in this area. My results, like those of many others reported at that time and subsequently, were entirely negative. A few investigators, however, claimed to have isolated a virus. Thus, Weir and Horsfall[5] produced a nonbacterial pneumonia in the mongoose and Eaton and his coworkers[6] described the propagation of a filterable agent in cotton rats and the embryonated egg. These observations have not as yet been confirmed by other workers.

By 1944 it was therefore obvious to most investigators that the agent of this disease was closely adapted to the human host — perhaps so closely adapted that it could not be established in any other animal species. Accordingly, the Commission on Respiratory Diseases[7] located during the war at Fort Bragg, North Carolina, undertook experiments in human volunteers with the objective of proving whether the agent was transmissible and filterable. The results of these elaborate and costly experiments leave no reasonable doubt, I believe, that atypical pneumonia in which none of the known bacterial, fungal, viral or rickettsial agents can be demonstrated is due to a filterable virus. In all, three experiments were carried out in which pooled sputums and nasal washings from patients with characteris-

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tic cases of atypical pneumonia were inoculated by the respiratory route into human volunteers. In the last two, the subjects were divided into three groups, one of which received material passed through a bacteria-retaining filter, another unfiltered washings and a third unfiltered material that had been autoclaved. A condition compatible with atypical pneumonia was produced in some of the subjects inoculated in all three experiments. For example, in the last experiment, the typical disease was caused in 3 of the 12 men who received filtrate and in 3 of 12 others who were given the unfiltered material. The incubation period following inoculation with filtered material was approximately fourteen days, and that with unfiltered material approximately seven days. None of the 18 men who received autoclaved material (the control group) developed the disease. Since in this last experiment in particular every precaution was taken to eliminate the possibility of spontaneous infection, the results may be accepted as indicating that atypical pneumonia is due to a nonbacterial, filter-passing agent.

It is of great interest, regarding the current epidemiologic views concerning atypical pneumonia, that 10 of the 24 men who received the unautoclaved material developed minor upper respiratory illness of an undifferentiated type, without signs of lung involvement, since it has been the opinion of clinical students of the disease that during epidemics many persons become infected with the virus who do not develop pneumonia but only mild upper respiratory symptoms. It should be pointed out, however, that whereas these results strongly suggest that the virus of atypical pneumonia frequently gives rise to a nonpneumonic type of infection, they do not prove that the same agent is responsible for both diseases, since the possibility of the presence of two viruses in the inoculum was not ruled out.

The Commission also concerned itself with the relation between two other frequent clinical types of acute respiratory illness and their etiologies. Thus, in additional experiments with 42 volunteers,[8] they inoculated material obtained from a person with symptoms mainly of coryza — that is, those of the common cold and with minimal signs of pharyngeal inflammation. Another group was inoculated with materials from a patient with an infection distinguished from the common cold principally by sore throat and little nasal involvement. The results indicated clearly that both these clinical types of infection could be experimentally transmitted to human beings by means of filtrates of throat washings. The most interesting finding, perhaps, was the difference in the incubation period of the two types of experimentally induced disease. The coryzal syndrome had an incubation period of one or two days — an observation in agreement with earlier work on the common cold by Dochez and others. In contrast, the disease characterized chiefly by inflammation of the pharynx had an incubation period of five or six days. It will be noted that both these periods of incubation were shorter than that of the experimental atypical pneumonia. Worthy of emphasis, too, is the finding that no immunity apparently resulted from the experimental coryzal infection, since reinoculation within three weeks with active material from patients who had recovered again induced the disease. On the other hand, the pharyngitis virus produced a specifically increased resistance following reinoculation. Neither the common cold nor the pharyngitic syndrome induced immunity against experimental inoculation of material containing the virus of atypical pneumonia. The participation of hemolytic streptococci or influenza virus in either type of infection was satisfactorily eliminated as a possibility.

In concluding this brief discussion of nonbacterial, acute respiratory disease, exclusive of influenza, it can be stated that although knowledge of these conditions is still distressingly chaotic, definite progress has been made toward an ultimate etiologic classification. Certainly, one can be reasonably certain that the nature of the etiologic agent in primary atypical pneumonia has been defined. The infection may be recognized not only by x-ray findings but also, in many cases, through the application of the test for cold agglutinins[9] or the Thomas agglutination test employing the indifferent streptococcus MG.[10] This information on etiology and on diagnostic aids indicates how much progress has been made in a very difficult problem within a short time. When suitable laboratory facilities are available, full advantage should be taken of them by physicians in the diagnosis of suspected cases of this disease.

Reimann's Epidemic Diarrhea

The occurrence of outbreaks of diarrheal disease, usually mild in character and acute in nature and lasting ordinarily twenty-four or forty-eight hours, has long been observed and has been reported in the medical literature from many parts of the world. The common enteric bacterial pathogens have often been conspicuously absent in such outbreaks, which are prone to occur in institutions such as schools, barracks and hospitals. The mild character of these epidemic gastrointestinal disturbances has been mainly responsible for the lack of efforts toward the elucidation of the responsible agent. Clearly infectious in their behavior, such epidemics do not appear to be occasioned by contaminated food, water or milk. This type of illness in adults, interesting enough in itself, has of late attained additional significance because of possible relations to the cause of the highly fatal diarrhea of the newborn that Clifford[11] has discussed. Accordingly, it seems pertinent to emphasize the studies in which Reimann and his associates[12] recently described and investigated an outbreak of epidemic diarrhea among medical students in Philadelphia. This epidemic was similar in all respects to many others that have

been recorded. In general, such outbreaks have had the following characteristics:

They tend to occur in the autumn but there are no strictly seasonal limitations.

Children and young adults appear to be particularly susceptible, but no age group is resistant.

The morbidity is high, ranging from 15 to 100 per cent.

Usually, there is no mortality.

The symptoms, which follow an incubation period of about two days in most cases, consist of anorexia, nausea, vomiting, diarrhea, dizziness, aching and abdominal discomfort or cramps. Not all these manifestations, of course, are always noted in the same person.

Fever is exceptional.

Occasionally, there are concomitant signs of mild upper respiratory disease, a fact that has sometimes been responsible for the diagnosis of so-called "intestinal flu." I have had occasion to follow the investigation of two outbreaks of epidemic diarrhea in state institutions during the last few months. In every respect they conformed in epidemiologic pattern and clinical picture to Reimann's outbreak, except that in a few cases of aged and sick patients the disease seemed to be a contributing factor to their deaths.

Because of the failure to incriminate any of the usual vehicles of transmission of enteric diseases of known etiology, Reimann and his associates[13] investigated experimentally in volunteers the hypothesis that this disease was communicable via the respiratory route. Thirty-two healthy young adults were permitted to inhale nebulized garglings obtained from patients with the typical symptomatology, after the material had been filtered to remove bacteria. Similarly, stool filtrates from patients with acute cases were administered in the form of a fine spray to 21 other volunteers. In each group approximately half the subjects developed symptoms of the disease. In most cases those who became ill did so one to four days after inoculation, thus giving evidence of the probable duration of the incubation period. Unfortunately, these experiments were carried out at a time when the epidemic, although definitely on the wane among the general student body, was still active, and since rigorous precautions for isolation were not possible, the results might be questioned. However, when one considers that the incidence of disease among the student body was only 9 per cent, as contrasted with 53 per cent among the inoculated subjects, there can be little doubt that in the majority of cases the disease had been induced by means of bacteria-free filtrate administered by the respiratory route. That the natural mode of transmission is probably by this route is supported by the fact that no symptoms developed in a number of volunteers who swallowed capsules containing filtrates of garglings or stools.

As yet there has been little work in attempting to isolate a virus in the laboratory from epidemic diarrhea. Reimann and his associates[14] failed to infect young mice and the chorioallantoic membrane of the embryonated egg. Experiments in our own laboratory are now being carried on with the purpose of investigating this problem more intensively. To my mind these observations of Reimann are of much significance not only because they seem to represent the best evidence so far presented that a virus can cause a characteristic enteric disease but also, taken with other recent information, because they strongly suggest that a whole group of similar agents are involved in various clinical types of acute gastrointestinal disorder.

Epidemic Keratoconjunctivitis

Epidemic keratoconjunctivitis is a disease that has long been known but in which the etiology has been obscure. First described by Fuchs in 1889, epidemics have subsequently occurred throughout the world. Not until 1941, however, was the disease reported in the United States, where it emerged as an epidemic in shipyards on the Pacific Coast.[15] Since that time cases have been described elsewhere in this country. In the East, outbreaks have occurred in the area around New York City,[16] in Connecticut and in western Massachusetts. It tends to be epidemic in industrial plants but may occur sporadically, and has been shown to be spread in physicians' offices and ophthalmic dispensaries where proper aseptic technics have not been employed.

The disease is characterized by nonpurulent inflammation of the conjunctivas, preauricular lymphadenitis and superficial punctate corneal opacities. There may be accompanying symptoms of headache, malaise and slight fever. The incubation period is unknown in the natural disease, which lasts from two to four weeks or longer. Recovery is usually complete, although in a small percentage of patients keratitis with impairment of vision may persist. Although earlier experimental work pointed to a filterable virus, it was not until the work of Sanders and Alexander in 1942[17] that the etiology was finally established. With conjunctival scrapings of 2 patients these investigators obtained a mild encephalitic disease following the intracerebral inoculation of white mice. More decisive results were obtained after the cultivation of mouse brain containing the virus in tissue culture with subsequent mouse passages. This somewhat unconventional procedure appeared to enhance the virulence of the virus for mice so that intracerebral inoculation was regularly followed by death. But subsequently, in 1945, Maumenee and his associates[18] isolated a strain of virus that was from the outset of high virulence for mice since it regularly killed these animals within three to five days after intracerebral inoculation.

The mouse-adapted strain of this virus was then cultivated in the embryonated egg by Calkins and Bond.[19]

The relation of the virus to the human disease was demonstrated in two ways by Sanders and Alexander[17]: instillation of a suspension of mouse brain into the conjunctival sac of a volunteer resulted in a modified but typical attack of keratoconjunctivitis; and patients recovering from the disease were shown to develop antibodies that specifically neutralized the virus. Such antibodies were not found earlier in the disease or in a number of normal human subjects. On the other hand, the pathogenicity of the virus for mice was not neutralized by antibodies against lymphocytic choriomeningitis, Theiler's mouse poliomyelitis and serums from patients suffering from nonspecific conjunctivitis or keratitis. These workers also found the virus to be distinct from the herpes virus on the basis of virus-neutralization tests with appropriate antiserums. Maumenee and his associates,[18] however, discerned an antigenic similarity between the virus of keratoconjunctivitis and that of herpes. In spite of this discrepancy in the findings of the two groups of workers the viruses are quite distinct, since animals actively immunized against herpes virus have been shown to be resistant to herpes but not to the epidemic keratoconjunctivitis virus. Moreover, significant differences in the size of the infective particles of the two viruses have been determined. The data indicating that the viruses can be distinguished from each other in the laboratory are important because the herpes virus, as is well known, can cause a conjunctivitis with involvement of the cornea that could be confused with that due to the virus of epidemic keratoconjunctivitis, although certain clinical features of herpetic keratoconjunctivitis are characteristic, such as the dendritic processes of the lesion. The lack of epidemic spread of herpetic conjunctivitis also represents an important differential feature. The clinical similarity is close enough, however, so that recourse should be had to a suitably equipped laboratory if a final etiologic diagnosis is to be made. So far as I know, epidemic keratoconjunctivitis has been a rare disease in Massachusetts, but the possibility exists that epidemics may occur at any time.

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Little or nothing has been said above regarding specific prevention or therapy, because there is as yet little or nothing to say regarding these always pressing concerns. But with the greatly increased interest and activity in the realm of viruses, it is by no means impossible that in the not too distant future one talking about the various categories of diseases exemplified by the infections I have discussed may have a different story to tell.

References

1. Humbert, W. C., Tucker, C. B., Mosley, K. T., and Bishop, L. K. Epidemic of acute meningo-encephalitis in Giles County, Tennessee: unusual disease. *Am. J. Pub. Health* **37**:564-569, 1947.
2. Commission on Acute Respiratory Diseases. Present status of etiology of primary atypical pneumonia. *Bull. New York Acad. Med.* **21**: 235-262, 1945.
3. Bock, A. V. Clinical observations, complications, and treatment of acute upper respiratory tract infections. *Ann. Int. Med.* **12**:317-322, 1938.
4. Murray, M. E., Jr. Atypical bronchopneumonia of unknown etiology possibly due to filterable virus. *New Eng. J. Med.* **222**:565-573, 1940.
5. Weir, J. M., and Horsfall, F. L., Jr. Recovery from patients with acute pneumonitis of virus causing pneumonia in mongoose. *J. Exper. Med.* **72**:595-610, 1940.
6. Eaton, M. D., Meiklejohn, G., and van Herick, W. Studies on etiology of primary atypical pneumonia: filterable agent transmissible to cotton rats, hamsters, and chick embryos. *J. Exper. Med.* **79**: 649-668, 1944.
7. Commission on Acute Respiratory Diseases. Transmission of primary atypical pneumonia to human volunteers. *Bull. Johns Hopkins Hosp.* **79**:97-167, 1946.
8. Commission on Acute Respiratory Diseases. Experimental transmission of minor respiratory illness to human volunteers by filter passing agents. I. Demonstration of two types of illness characterized by long and short incubation periods and different clinical features. II. Immunity on reinoculation with agents from two types of minor respiratory illness and from primary atypical pneumonia. *J. Clin. Investigation* **26**:957-982, 1947.
9. Peterson, O. L., Ham, T. H., and Finland, M. Cold agglutinins (autohemagglutinins) in primary atypical pneumonias. *Science* **97**: 167, 1943.
10. Thomas, L., Mirick, G. S., Curnen, E. C., Ziegler, J. E., Jr., and Horsfall, F. L., Jr. Serological reactions with indifferent streptococcus n primary atypical pneumonia. *Science* **98**:566-568, 1943.
11. Clifford, S. Diarrhea of newborn: its causes and prevention. *New Eng. J. Med.* (in press).
12. Reimann, H. A., Hodges, J. H., and Price, A. H. Epidemic diarrhea, nausea and vomiting of unknown cause. *J. A. M. A.* **127**:1-6, 1945.
13. Reimann, H. A., Price, A. H., and Hodge, J. H. Cause of epidemic diarrhea, nausea and vomiting (viral dysentery?) *Proc. Soc. Exper. Biol. & Med.* **59**:8, 1945.
14. *Idem.* Negative results in studies of epidemic diarrhea, nausea, and vomiting of unknown cause. *Proc. Soc. Exper. Biol. & Med.* **55**: 233, 1944.
15. Hogan, M. J., and Crawford, J. W. Epidemic keratoconjunctivitis (superficial punctate keratitis, keratitis subepithelialis, keratitis maculosa, keratitis nummularis), with review of literature and report of 125 cases. *Am. J. Ophth.* **25**:1059-1078, 1942.
16. Sanders, M. Epidemic keratoconjunctivitis ("shipyard conjunctivitis"). *Arch. Ophth.* **28**:581-586, 1942.
17. Sanders, M., and Alexander, R. C. Epidemic keratoconjunctivitis. I. Isolation and identification of filterable virus. *J. Exper. Med.* **77**: 71-96, 1943.
18. Maumenee, A. E., Hayes, G. S., and Hartman, T. L. Isolation and identification of causative agent in epidemic keratoconjunctivitis (superficial punctate keratitis) and herpetic keratoconjunctivitis. *Am. J. Ophth.* **28**:823-839, 1945.
19. Calkins, H. E., and Bond, G. C. Adaptation of virus of epidemic keratoconjunctivitis to development in extra-embryonic fluid of chick embryo. *Proc. Soc. Exper. Biol. & Med.* **56**:46, 1944.

MEDICAL CARE FOR THE PEOPLE OF MASSACHUSETTS: THE CONTRIBUTION OF BLUE SHIELD*

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THERE are now fifty-seven medical-care plans sponsored by medical societies and operating in thirty-three states. They cover approximately 4,500,000 persons. Fifty-five of these plans are nonprofit; the other two utilize the services of commercial insurance carriers. In the fifteen states that do not have plans in operation, nonprofit plans are being organized in seven, commercial plans are being organized in three, and preliminary discussions are under way in four. This leaves but one state in which nothing tangible is being accomplished.

Much of the credit for this remarkable picture must go to the Council on Medical Service of the American Medical Association, which since its creation in 1943 has not only prompted the establishment of plans in many areas but also given marked impetus to the medical-care-plan movement as a whole.

Although well able to carry on its promotional functions, the Council early realized that it was not in a position to cope with the technical aspects of development and co-ordination. Consequently, about a year ago, it sponsored a meeting of plan executives, out of which came an independent organization known as Associated Medical Care Plans. Between annual meetings of the members, the affairs of this association are directed by a nine-man commission that includes three representatives from the Council on Medical Service.

Although there is necessarily some overlapping of the interests and activities of the Council on Medical Service and the Commission of Associated Medical Care Plans, the Council is primarily concerned with promoting the establishment of plans and determining broad concepts of policy that should characterize the prepayment movement. The Commission, on the other hand, is primarily occupied with the day-to-day problems of plan organization and operation and with interplan relations.

Of the sixty-two nonprofit plans now in operation, or about to operate, forty-one are members of Associated Medical Care Plans, and it is expected that the remaining twenty-one will become members in the very near future. Although not specifically excluded, it is highly unlikely that any commercial plan will be admitted to membership.

With nearly 600,000 persons covered, Massachusetts Medical Service (Blue Shield) is the second largest and one of the most successful medical-care plans in the nation. In retrospect, the primary reasons for these achievements are not hard to find and may be briefly summarized as follows:

The Board of Directors is made up of one third physicians and two thirds laymen. Lay representation is almost equally divided between the population segments broadly defined by the terms labor and management. In the conduct of a million-dollar enterprise, it is absolutely essential that provision be made for guidance by trained businessmen. Similarly, in any organization that deals directly with hundreds of thousands of persons it is essential that certain of their attitudes be constantly appraised by experts in such matters.

All rules and regulations pertaining to medical relation must be initiated by the physicians on the Board and approved by the Executive Committee of the Council of the Massachusetts Medical Society. It is now generally acknowledged that in any kind of medical-care program, determinations concerning medical matters must be delegated to the physicians involved.

Income limits, below which members are entitled to service benefits without additional charge, must be approved by the Council of the Massachusetts Medical Society. The level at which income limits are established is a direct measure of the willingness of the medical profession to assume a fundamental sociologic obligation on behalf of persons in the low and moderate income groups and therefore has a direct influence on sales resistance and the attitude of the public toward the profession. Consequently, it is of the utmost importance that these determinations be based on enlightened professional self-interest. When Massachusetts Medical Service was established, approximately 80 per cent of the wage-earning population of the Commonwealth was in the under-income category. With increased earnings during the war, this figure fell to 65 per cent, where it remained until recent action of the Council raised the limit for the family to $3000 and thus restored the original relation, which, incidentally, is becoming recognized as standard for the nation.

Physician participation, initially in the neighborhood of 50 per cent, has steadily increased to its present level of more than 90 per cent. With payments for services by nonparticipating physi-

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cians within the Commonwealth virtually excluded, it is absolutely essential that a large percentage participate and that they be well distributed throughout the Commonwealth; otherwise the plan degenerates into a straight cash-indemnity arrangement.

The administrative relation with Massachusetts Hospital Service, Incorporated (Blue Cross) has been eminently successful. Below the policy-making level there is practically no discernible distinction between the two organizations.

As presently constituted, Massachusetts Medical Service (Blue Shield) provides benefits only for surgical and obstetric services rendered in the hospital. On June 1, 1947, this program will be extended to include benefits for medical (nonsurgical) services rendered in the hospital and for surgical and obstetric services rendered outside the hospital. Inclusion of benefits for medical (nonsurgical) services rendered outside the hospital is not anticipated in the immediate future because this type of coverage is financially hazardous unless undesirable coinsurance features are imposed or unless subscription rates are increased beyond the present point of public acceptance.

Implementation of any program directly affecting the public is bound to arouse a crossfire of conflicting interests. Difficulties both predictable and unpredictable arise. Nevertheless, if such a program is to survive and prosper in a democracy, its difficulties must ultimately be resolved in the interest of the public.

Many studies made during the past few years have indicated that the American people favor prepayment of the cost of medical and hospital care. Acknowledging this interest, the American Medical Association and its constituent societies are now committed to the principle of prepayment, with the reservation, however, that it be developed under voluntary auspices. With the imposition of this qualification, the medical profession assumed a tremendous obligation.

To meet this obligation, medical societies have set up their own prepayment plans in thirty-one states. In two other states the societies have called upon commercial insurance carriers. The only point of distinction between the prepayment movement as it developed in Great Britain and on the Continent and as it is being developed here is that the medical profession in the United States has sought to meet its own responsibility without the interposition of a third party imbued with interests foreign to the basic concepts that characterize medical practice. Should a wholesale tendency on the part of physicians to hand over their acknowledged responsibility to commercial carriers at any time develop, it is safe to predict that American medicine will quickly fall into the hands of the Government.

Although it may be assumed that medical-care plans sponsored by medical societies will be in operation in all states in the near future, it would be fatal to assume that the obligation of the medical profession will thereby be resolved. To establish a medical-care plan is one thing; to keep it operating on a satisfactory basis is another.

Up to the present, Massachusetts Medical Service (Blue Shield), which is one of the older plans, has encountered no serious problems, mainly because the number of plan patients that any given physician may see is not large. However, the picture is now rapidly changing. Present enrollment is in the neighborhood of 600,000 persons, and it seems safe to predict that by this time next year the figure will reach 1,000,000 or more. The result is that previously casual professional relations are becoming less casual as more and more physicians come to realize that by its very nature an expanding medical prepayment plan, while solving many problems, introduces new ones. From his own economic standpoint, for instance, it becomes increasingly incumbent upon the physician to establish a routine that will effectively identify plan patients and establish their income status. Similarly, from the standpoint of the plan patient, a routine of this sort must be developed if confusion and delay, with consequent ill feeling, are to be avoided.

Fortunately, the vast majority of problems that arise lend themselves to reasonable solution. Nevertheless, they frequently require professional concessions, which must be made if the program is to accomplish its objectives and satisfy rational public demands. Massachusetts Medical Service (Blue Shield) is an organ of the Massachusetts Medical Society. Its board of directors is elected by the Executive Committee of the Council. Every physician has a direct voice in its affairs through his district professional service committee. Its problems are the problems of the profession, and its success or failure will largely be determined by professional attitudes now in the process of development.

REHABILITATION OF THE EMPLOYEE INJURED IN INDUSTRY*

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IN THE life of the average workingman there is nothing more serious than the loss of his earning capacity. A serious injury with prolonged disability has far-reaching effects, not only on the man himself but also on his family. Plans for the purchase of a home and for education of his family are uppermost in the minds of most workingmen — plans that may have to be abandoned as a result of an industrial accident. It is only natural, therefore, that a person so injured should look to his doctor for the treatment that will restore him to his job in the best possible condition in the shortest possible time. It is clearly the physician's duty to give his very best from the minute of injury until the patient can return to work.

In the past few years progress in the treatment of traumatic lesions has come largely through the perfection of technics in the handling of the acute emergency. In this regard tremendous strides have been made. Most men who have kept abreast of the literature and who are aware of the modern methods of treatment can handle the acute emergency with competence. Treatment when the emergency is over, however, leaves much to be desired.

All physicians are more or less x-ray conscious and are apt to be most concerned with the roentgenographic appearance of the patient's lesion. However, we are likely to be entirely oblivious of the physiologic, pathologic and mental changes that may be developing in the patient. Failure to recognize such changes, produced by immobilization and enforced recumbency, may seriously delay the recovery of patients who have had efficient treatment in the emergency. Until these changes are recognized they cannot be prevented, and the patient's convalescence will be extended. Inadequate aftercare is one of the great weaknesses of present-day surgery.

The first of the complications or changes that must be prevented is atrophy. When a patient is forced to remain in bed, all the tissues, particularly skeletal muscle, undergo atrophy. The second change is joint stiffness. The longer the period of recumbency, the more extensive atrophy and joint stiffness become. We have all seen patients too weak to sit up and too stiff to walk when their injuries have sufficiently healed to allow them to do so. This leads to further recumbency and the development of a vicious circle. Unfortunately, this condition is not uncommon and is a definite reflection on present-day treatment. General body and muscular tone can be maintained and joint stiffness prevented if patients perform simple exercises while in bed. There is usually no reason why such exercises cannot be performed in parts remote from the site of injury. The exercises not only benefit the patient physically but also help develop a feeling of well-being and, of utmost importance, help to bolster morale. Such exercises must not be left to the patient. The physician must see to it that these exercises are done, and done intelligently. By such means, the period of disability can be cut down and the patient's physical condition improved when he is ready to become ambulatory.

When it is necessary to splint a part, atrophy is much more rapid and extensive, and joint stiffness more likely to occur. Therefore, in splinting, only the minimum immobilization must be used. Parts uninvolved must be kept free so that they can be exercised. One of the most troublesome complications of fractures of the upper extremity — the "frozen shoulder" due to carrying the arm in a sling — can be readily avoided if the patient simply lifts his arm over his head in flexion and abduction several times a day. This can be done without risk in fractures, once the part is adequately immobilized.

If there is persistent swelling of a part, the excess lymph in the tissues leaves a deposit of fibrin that, in time, is replaced by granulation tissue. Granulation tissue is scar tissue, and scar in the vicinity of a joint means loss of motion, particularly if the joint requires immobilization. This is of the utmost importance in injuries of the hand and wrist, in which swelling of the fingers is likely to occur. When such injuries require splinting, only the minimum splinting must be used. Casts applied for injuries of the forearm and wrist should not extend beyond the distal palmar crease, so that the fingers can be mobilized. When fingers must be splinted the position of flexion should be used whenever possible to put the collateral ligaments of the fingers under tension. To allow the ligaments to stiffen and contract in the position of extension means long and tedious work in the restoration of flexion. About 25 per cent of cases at the Liberty Mutual Rehabilitation Center are hand injuries, and many of these patients are under treatment for stiffness of the fingers that, with proper immobilization, could have been avoided.

When the lower extremity requires immobilization, muscle tone can still be largely preserved by

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the simple process of muscle setting within the splint or cast. This can be done without jeopardizing the healing process in all conditions, with the possible exception of fresh tendon sutures.

By exercising the body as a whole while the patient is in bed and by exercising uninvolved parts and by muscle-setting exercises while he is in splints, much can be done to preserve general and local muscle tone and joint mobility during the period of recumbency or immobilization.

When the patient is freed of all apparatus and is ambulatory the job is by no means over. This is in all probability the most critical period of all, because failure to use the injured part can still nullify all the good work done in the period of immobilization. When a patient is at home he is no longer under complete supervision and is apt to neglect his exercises. Trips to the doctor's office three times a week for baking and massage make a dangerous rut for the patient to get into. Between these trips he is likely to do nothing for himself and to let the physician or a physiotherapist do the work for him.

Patients must be made to understand that the doctor or his physiotherapist can aid them in the restoration of strength and motion, but that the actual work must be done by themselves. Exercises must be performed even though they cause some discomfort. However, it is the duty of the physician to make sure that a definite course of action is adopted and understood. The patient must know exactly what exercises he is to do, how long he must do them and why he is doing them. Too often, progress is slow because the patient does not do the exercises properly if at all. This is often due to the fact that the doctor has not given sufficient instruction and has not checked to see that the instructions have been carried out. Routine gymnastic exercises are dull and uninteresting, and often do not accomplish the desired result. Exercises in the form of work therapy are much more beneficial. A patient with a saw and hammer can accomplish more for himself in one week than all the baking and massage can perform in months. Work or occupational therapy is a form of treatment that has been completely overlooked and that everyone interested in the treatment of traumatic lesions must learn. Occupational therapy does not mean the making of leather belts, pocketbooks and so forth, which have a place in some conditions but are chiefly diversional and of little value to the average worker, but actual work designed to restore to the patient motions essential in his trade. Frederic J. Cotton once said, "The best way to restore a bricklayer to his job is to make him lay bricks." This statement is undeniably true, but such therapy is not always so simple as it sounds.

Patients who have had prolonged and painful disability are apt to suffer from mental depression or loss of morale. Failure to notice improvement favors the development of many psychogenic factors, particularly an anxiety state. Fear of being unable to return to their regular work and fear that they have lost their jobs after a prolonged convalescence are common causes of mental depression and loss of morale. This state is aggravated by domestic and financial difficulties, brought on by the loss of earning power. Occasionally, this condition is precipitated or aggravated by the development of the menopause. Such patients are extremely difficult to rehabilitate. They need encouragement and must often be convinced that they are not quite so badly off as they think. For such a person there is no better treatment than work therapy.

Dissatisfaction with present methods of treatment and encouragement offered by the rehabilitation program developed in England during the war brought about the establishment of the Rehabilitation Center by the Liberty Mutual Insurance Company in June, 1943. In the past four years we have become convinced of the value of a combination of physiotherapy and occupational therapy, and the decided advantage of keeping the patient busy all day long for five days a week.

When a patient is admitted to the Center a complete appraisal is made. The exact extent of the injuries is determined. If it is believed that he can be rehabilitated, that further surgery is not indicated and that the general physical condition is satisfactory, treatment is started.

Usually, the patient is sent first to the physiotherapy department, which is completely equipped with the usual armamentarium of infrared lamps, diathermy, whirlpool baths, paraffin baths, stall bars, chest weights, Kanavel tables, graduated stairs, resistance bicycles, rowing machines and so forth. Here he is placed on daily exercises that are performed under supervision.

When he has improved sufficiently he is sent to the occupational-therapy department, where he is given work to exercise the disabled part. Tools and sanding blocks are constructed to fit the individual needs of the patient. All work is planned and supervised. Care is taken not to exceed the fatigue point. At first only light or sedentary work may be done. As the work tolerance increases, the work load is increased. Since most of these patients are unskilled, woodworking is the chief means of work therapy. No motor-driven tools are used. Jig saws are operated by sewing-machine or bicycle jigs. For ankle injuries the sewing-machine jig and for knee injuries the bicycle jig are used. Foot-operated grinding wheels are also of value. For shoulder injuries suspension slings aid in elevation of the arm. When a shoulder has improved sufficiently a hand-operated printing machine is of value. Painters are allowed to paint and thus to exercise their shoulders, hands and wrists. There is a complete machinist's outfit. Logs for sawing and a sand pit are used to build work tolerance in laborers. Hand saws, planes, files and the usual carpenter's equip-

ment are of great value in restoring lost motion and muscle power, especially in the upper extremity. To keep the patient's interest, definite work projects are created. The building of such objects as end tables, sewing cabinets, tool boxes, rocking horses, carts, chairs and magazine racks holds the patient's interest. Knot tying, rug making, modeling in plaster and work carving are of value in hand cases. All work can be done at any level and in any plane, so that any lost motion and any atrophied muscle group can be restored.

When a patient has reached his work tolerance he is allowed to rest. At that time he can listen to the radio and, especially in the summer months, to the ball games.

After the rest period he is sent to the recreational-therapy department. He may play pool, ping-pong, horseshoes, darts, checkers and so forth. Recreational therapy is also designed to aid in the restoration of lost motion. For example, checkers may be played on the floor, on a table or on the wall. Ping-pong has been found to be of considerable value in the training of patients with upper-extremity amputations. The agility that can be developed in a short time by this means is remarkable.

The patient, it can be seen, is kept busy all day long for five days a week. The building of articles in the workshop is a tremendous stimulus and does much to raise morale. Patients become so engrossed in their work that they must be carefully watched so that they do not become fatigued. Women are as enthusiastic as men. A spirit of competition is developed between patients with similar injuries. Disgruntled and discouraged patients soon enter into the swing of things and rapidly lose their complaints. Under such a regime most patients make progress both physically and psychologically. It is not uncommon for patients to say, "If I can do this work I can do my own." Most patients, convinced in their own minds that they can return to work, need no further stimulus to do so.

The following statistics give some idea of our success (Table 1). In the past four years 666 cases have been treated. Of this number there were 540 male and 126 female patients. The average age is higher than one would expect, being forty-six years for men and forty-three years for women. Most of these patients had multiple and serious injuries. With such injuries, in this age group, the earlier treatment is started, the better the result. In the average case, however, six and a half months had elapsed between the date of injury and admission to the Center. Much valuable time had thus been lost. Atrophy, joint stiffness and loss of morale have usually been well advanced and have been serious handicaps to overcome. Despite this fact, however, 368 patients, or 65 per cent of all patients admitted, have returned to gainful employment. The average length of treatment required has been forty-two days.

Table 1. *Results of Therapy at Rehabilitation Center, Liberty Mutual Insurance Company from June, 1943 to April, 1947.*

Total Patients	Male Patients	Female Patients	Average Age		Average Interval from Injury to Admission	Average Period of Treatment	Patients Returned to Work	
			Male patients	Female patients			No.	Percentage
			yr.	yr.	mo.	da.		
666	540	126	46	43	6.5	42	368	65

Considering the seriousness of the injuries, the age of the patients and the extent of the complications produced by the lack of efficient treatment for six and a half months, it is doubtful that many of these patients could have been rehabilitated by any other means.

Our experience has convinced us of the value of a combination of physical therapy and early work therapy. With the education of the medical profession in the procedures of treatment and after-care described above, it is believed that a far greater number of seriously injured workmen will be restored both to industry and to their families.

MEDICAL PROGRESS

CUTANEOUS MEDICINE

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THE skin pictures the general health of the patient much better than any other organ. Age is reflected in the pink bloom of infancy, the oiliness and pasty appearance of adolescence, the disfiguring yellowish spots and telangiectasia of middle age and the wrinkled, thin, overstretched and dry appearance of old age. Physicians of previous generations trained their powers of observation and palpation and carefully studied changes in the skin and mucous membranes; many diagnoses of systemic diseases resulted from their keen perception. Today, physicians fail to make use of these facilities and depend too much on mechanical devices and laboratory procedures, many of which are irrelevant or unnecessary; they piece the data together like a picture puzzle.

Fortunately, many clinicians exercise their powers of observation of the skin, for they have learned that such study yields important clues in the diagnosis of systemic disease. Bacteriologists, pathologists, roentgenologists and even anatomists are showing increased interest in dermatology.

An anatomist states that a clinician displays keen clinical discernment when he regards the skin as an index to visceral change as well as subject to dermatologic conditions. To adopt this point of view is to accept the embryologic fact that the skin is an exposed part of the depressed central nervous system or, conversely, that the central nervous system is a depressed part of the skin. Thus, itching or seborrheic dermatitis may be due on the one hand to a specific dermatologic condition and on the other hand to an inherited predisposition of the autonomic nervous system, the gonadal system or the central nervous system. It is this developmental point of view that makes possible the consideration of the skin as an integral part of the organism.[1]

No one believes that systemic disease can be diagnosed entirely from the skin, but careful observation can be extremely valuable. Redness of the face may suggest an irritable heart, capillary and arterial pulsation, an aortic insufficiency, cyanosis of the face, a paroxysmal tachycardia, malar flush, a yellowish forehead and blue lips, a mitral stenosis, and petechial spots and pinkish, tender macules on the fingers and toes, an endocarditis. The earthy hue of the skin tinged with blueness suggests an emphysema.

Many a systemic disease produces a cutaneous change in the initial or final stages. Many a clinical report starts with the statement that the patient first noticed spots on the skin. These occur so frequently and disappear so rapidly that they may have no clinical significance, except to suggest a certain category of disease, especially the infections. In fatal diseases the skin may give the first warning, as in pruritus or the pigmentary eruptions often seen with internal malignant tumors. Later, the inflammatory lesions may precede metastases. A patient under observation following extirpation of the vulva for removal of a cancer showed nodules and later small bullae preceding a necrotic crusted center that histopathologically revealed carcinomatous changes.

The dermatologist has known for centuries that, apart from the dermatitides due to chemical irritants, parasitic infestations and bacterial and fungous infections, most cutaneous diseases are associated with systemic disturbances and that many systemic diseases affect the skin. A dermatologist must have the diagnostic acumen of the internist as well as the patience and therapeutic skill of the "externist." He realizes that treatment must be not only local but also systemic if the contributing or precipitating cause is to be removed.

GENETICS

Abnormalities due to defects of the germ plasm may manifest themselves very early. In albinism a deficiency in pigment may be complete or incomplete. Xeroderma pigmentosa may be suspected by the photophobia noticed in the first few weeks of life and later by erythema, pigmentation, freckles, atrophy, telangiectasia and malignant growths. Hereditary hemorrhagic telangiectasia (Rendu–Osler–Weber's syndrome) may affect several members of a family.[2]

Photodermatosis, with or without circulating hematoporphyrin, is receiving considerable discussion, and it is now fairly well recognized that the porphyria is the result and not the cause of the dermal sensitization.[3]

Lipoid proteonosis is a familial disease first described in 1929 by Urbach.[4] It begins in infancy,

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with hoarseness and inability to cry. Various skin-colored, nodular, hyperkeratotic or warty lesions appear on the face, extremities and mucous membranes. Hypertrophic plaques may be present on the elbows and knees. Diabetes is sometimes associated with this disease. The blood lipoids are essentially normal, but there is a disturbance of the phospholipids.

I have seen xanthoma tuberosum multiplex in more than one member of a family. It is due to a hypercholesteremia of the blood, and the patient usually presents yellowish nodules on the buttocks and extensor surfaces. Other members of the family may have diabetes or hypercholesteremia, or both.

Disturbances of the elastic tissue manifest themselves in hyperelasticity and fragility of the skin, hyperelasticity of the joints, pseudo-tumors following trauma and subcutaneous nodules (cutis hyperelastica, Ehlers–Danlos syndrome), and deficient elastic tissue is seen in epidermolysis bullosa. This condition may vary from a mild disturbance of the skin with the occasional bullae following trauma to a severe type with not only cutaneous and mucous membrane lesions but also loss of hair and low intelligence. It may produce such severe systemic disturbances as to mislead dermatologists into describing the disease under another name.

Danbolt and Closs[6] classified 2 cases by the title "akrodermatitis enteropathica" and attributed the affection to disturbances of the gastrointestinal tract. The disease is characterized by a pustulous dermatitis, which is frequently familial and appears in early childhood, often after weaning. The dermatitis is preferentially located around the natural openings of the body and on the protruding parts of the head, trunk and extremities (hence the term "akrodermatitis"). The terminal phalanges of the fingers are swollen, and there is pustulous paronychia and atrophy of the nails. Furthermore, there are total alopecia, photophobia and blepharitis and sometimes affections of the mucous membrane of the oral cavity (papillomas of the tongue). The disease tends to be chronic, with recurring exacerbations, during which there is diarrhea with foamy, foul-smelling, pale yellowish-gray stools. The calcium and phosphorus content of the urine is pronouncedly diminished.[6]

The above disease is the severe type of epidermolysis bullosa originally described by Wende[6] in 1902, when he reported a case presenting unusual features. The chief characteristics were as follows: evidence of formation of vesicles and blebs at points subject to trauma and irritation; marked infiltration of the skin after the lesions subside; arrangement of the bullae in concentric patches; decided changes in the nails; lack of hair growth on the scalp and absence of eyelashes and eyebrows; and general tenuity of the skin. I have observed 2 children with this disease both of whom died. One showed pathogenic yeast cells on the perioral and perianal skin.

Keratosis follicularis (Darier's disease) has received more than passing interest because of claims for cure by the administration of vitamin A. I have observed no such cure in my cases, although all patients showed temporary improvement. This disease, which is transmitted by a single dominant, is usually limited to two generations because of infertility.

Thannhauser[7] disagrees with Cole's diagnosis of congenital ectodermal dysplasia associated with congenital cataracts. The former believes that the cases described are examples of Rothmund's syndrome due to defects of the entire germinal plasm. Cole[8] retaliates by citing Thannhauser's report of a typical anhydrotic type of ectodermal dysplasia with low fasting blood sugar, a flat sugar-tolerance curve and low blood pressure (disturbance of the adrenal medulla). Roentgenograms showed exostoses of the tables of the skull.[7] Osseous tissue is of mesodermal origin, and this case was not one of purely congenital ectodermal dysplasia of the anhydrotic type. Cole[8] states that he had difficulty in putting such a case under the proper heading from the developmental standpoint if the term "congenital ectodermal dysplasia" is to be used. Good proof of this contention is afforded by the fact that it is difficult to separate the ectoderm from the rest of the anatomy.

Carleton[9] described a case that was stated to be one of poikiloderma vasculare atrophicans, associated with cataracts (Rothmund's syndrome). Scleropoikiloderma has been mentioned as one of the characteristics of Werner's syndrome. Thannhauser,[10] however, believes that the features of the skin changes are different in both syndromes. In Werner's syndrome the most striking characteristic is tightening of the skin over the underlying structures, which are very poor in subcutaneous fat tissue. Ulcers develop mainly on the points of pressure on the heels and toes, over the ankles and especially over the Achilles tendon.

Moehlig[11] reports a case of progeria (premature old age) with severe dwarfism and congenital cataracts in a five-year-old boy who, although mentally retarded, had an unusual talent for music. This condition (Werner's syndrome) is seen in adults, and the cases are thought to be due to multiple germ defects.[11]

Neurofibromatosis (Von Recklinghausen's disease) has been traced by Frank[12] through five generations. This is a familial disease in which the defect may be transmitted in the same pattern — namely, one family showing areas of pigmentation and others, tumors of various size present also in the peripheral nerves. It may be associated with alopecia, feeblemindedness, epilepsy and dementia praecox. The pathogenesis of osteitis cystica localisata and disseminata is closely related to neurofibromatosis Recklinghausen and its osseous manifestations.[12] Von Recklinghausen's disease is a fairly common

one, which manifests itself in many strange combinations — for example, pigmentation and scoliosis. Its etiology and pathology are still open to discussion. Bourneville's disease occasionally resembles neurofibromatosis. The patient shows reddish, warty tumors, with feeble-mindedness or epilepsy. The tumors on the skin are of the adenoma sebaceum type, and these lesions may appear in the brain, heart or kidneys, resulting in death.

Endocrines

Many dermatologic manifestations have been attributed to endocrine dysfunction. A definite relation has been established in a few but has not been proved in others. The former are those associated with Addison's disease, adrenal tumors, Simmonds's disease, Cushing's syndrome, Frölich's syndrome, the Lawrence–Moon–Biedl syndrome and pancreatic disease. The others range from urticaria to psoriasis. As the result of improvement coincident with or subsequent to hormonal therapy, entities ranging from hypertrichosis to lupus erythematosus have been considered as due to endocrine diseases. Many apparent cures have not been corroborated.

Acne occurs with sufficient frequency in conjunction with changes in the endocrine system — as at adolescence, or with tumors of the adrenal cortex and arrhenoblastoma and also during the administration of androgens — to postulate a relation, but therapy as the result of these observations has not been too successful. Pruritus vulvae, kraurosis vulvae and leukoplakic vulvitis are apparently related to estrogen deficiency, but the clinical response is not startling. Hyperkeratitis (keratoderma) of the palms and soles associated with menopause may respond dramatically to sufficient estrogens. The pigmentation of the skin and mucous membranes in Addison's disease is characteristic and clears with suitable therapy. Calcinosis, local or generalized, may appear with hyperparathyroidism. Many cutaneous lesions have been attributed to diseases of the thyroid gland.

The dermatologist may be the first to diagnose myxedema. First consulted for loss of hair, he may note the dry, yellowish, waxy appearance of the skin, with extensive telangiectasia on the cheeks producing abnormal redness. The hair is dry, brittle and sparse, with considerable loss of the eyebrows, especially at the outer third. A lowered basal metabolic rate and a high cholesterol content confirm the diagnosis. Lange[14] states that the presence of edema in the skin of patients suffering from myxedema and the tendency to generalized serous effusions are so far physiologically unexplained. Five cases of myxedema all showed a marked increase in capillary permeability. With thyroid therapy the permeability rapidly returns to normal, simultaneously with a marked diuresis.[14] Amersbach and Kanee[15] reported that localized myxedema of the tuberous variety developed in a patient who had been suffering from exophthalmic goiter for four years and who had persistent hyperthyroidism, despite protracted therapy, including two thyroidectomies.

Pillsbury and Stokes[16] have described circumscribed forms of the disease. They analyzed 22 cases in the literature and 1 case of their own of circumscribed myxedema of the skin, and divided them into two classes: those characterized by nodular infiltrations variously distributed on the face, arms, back and scrotum, and those in which the manifestations of the skin are invariably associated with exophthalmic goiter. A tuberose nodular or papular type and a plaque type of myxedema of the skin involving the pretibial region are recognized.

O'Leary[17] reported a number of cases of localized solid edema of the extremities in association with exophthalmic goiter. In the majority of cases circumscribed myxedema follows thyroidectomy, appearing simultaneously with the signs and symptoms of recurrent hyperthyroidism. Sunseri[18] agrees that it may develop before thyroidectomy or before or during the active manifestations of thyroid intoxication.

The assumption that the thyroid hormone plays a role in the healing of wounds was corroborated by the fact that wounds heal poorly and sometimes not at all in myxedematous patients. Eppinger[19] first used aqueous extracts of thyroid gland mixed with lanolin, and then found that pulverized thyroid substance simply strewn into the wound was quite as effective. He believes that many torpid cutaneous ulcers are due to local myxedema.

I have noted an extensive isinglass scaling on the anterior aspect of the lower legs of several women with hypothyroidism. In hyperthyroidism the dermatologist may observe a markedly flushed, terrified, emaciated person whose skin is soft, oily and moist; hyperhidrosis and urticaria may be the chief complaints. Lichen planus with recurrent attacks associated with exacerbations of hyperthyroidism was reported by Ebert and Otsuka.[20] A patient with hyperthyroidism may be so sensitive to sunlight that exposure of a few minutes produces severe reddening of the skin and blistering.

Just as the appearance of the patient with myxedema is easily recognized by the physician, so also is that of the acromegalic patient. The skin of the sufferer from pituitary dysfunction, however, may be raised in folds, especially in the scalp, causing cutis verticis gyrata. Weber[21] stresses this relation and tabulates 12 cases. The hair is thick and coarse, as is the skin, which may be pigmented and freckled owing to melanin, especially in women. The plethoric skin, together with reddish or purplish abdominal striae, and painful adiposity should suggest Cushing's syndrome.

Within the past two years I have seen 2 cases of Simmonds's disease (pituitary cachexia), 1 in a

man, although most cases occur in females. Before death the patient showed complete loss of hair. Although he was in his late forties, the skin was smooth, thin and as delicate as a baby's, with a pale yellowish waxy color. The other patient showed a dry, coarse skin typical of hypothyroidism, with sparseness of the hair and with vegetating, crusting and scaling of the eyebrows, nose and lower legs. The plaques on the lower legs were finally cast off like pieces of bark from a tree. The diagnosis was made by laboratory findings, and therapy resulted in remarkable recovery.

Without corroboration, many diseases, including furunculosis, acne and psoriasis,[22] have been attributed to disease of the pancreas. A routine urinalysis is a necessity for a complete dermatologic diagnosis when there is only the complaint of pruritus. Deficiency of the islets of Langerhans may result in many cutaneous entities, such as necrobiosis lipoidica diabeticorum, xanthomatosis diabeticorum and hemachromatosis and such nonspecific manifestations as gangrene, ulcers and bacterial and Monilia infections.

Urbach[23] has recently suggested the term "skin diabetes" to designate the syndrome of "therapy-resistant skin disease (generally presenting the clinical picture of furunculosis, sweat gland abscesses, eczema, pruritus), high fasting skin sugar level together with a normal blood-sugar curve, and pronounced improvement of the dermatosis, as well as fall in high skin sugar level on a low carbohydrate diet, sometimes combined with insulin." His conclusion is as follows:

> Quite aside from the question as to whether or not cases presenting independent cutaneous glycohistechia are actually to be regarded as cases of skin diabetes, it may be safely said on the basis of clinical experience that a diabetic diet should unhesitatingly be tried in cases of therapy-resistant skin diseases such as furunculosis, eczema, or pruritus, even when the blood-sugar tolerance test is normal.

Sheppard[24] has reported stomatitis, burning, ulceration, dryness and many tongue symptoms.

Allergy

Allergy has become a too popular word in dermatology and medicine. It is time to review von Pirquet's[25] original article, in which he states:

> We need a new, general, and unambiguous word for the change of condition which the organism undergoes through contact with some organic, animate, or inanimate poison. The vaccinated person is in a different relation to the pox or lymph; the syphilitic, in a different relation to the syphilis organism; the tubercular person, in a different relation to the tuberculin; and the person injected with serum, in a different relation to the serum than are the individuals who have not yet come in contact with the agent concerned. Nevertheless he is still far from being unsensitive. All that we can say of him is that his capability of reaction is changed. For this general idea of changed reaction capability I propose the word allergy (allos designates the deviation from the original setup; that is, the deviation from the normal conduct). The vaccinated one, the tubercular, the person injected with the serum are with regard to their respective foreign bodies allergic. A foreign body, on the other hand, which influences the organism by means of incorporation (one or several times) to a change of reaction is an allergen. To the allergens belong not only the antigens but also the numerous albuminous bodies which cause no antibody formation but cause hypersensitivity. All inciters of infection sicknesses which are followed by immunity are allergens.

Several years ago, after listening to a symposium on allergy and dermatology, I defined allergy as follows: "In the field of practical dermatology, allergy is an intellectual hobby limited only by one's powers of expression, oral or written."[26] The term "allergy" may be accepted according to the definition of a specific altered capacity to react if the causative factors can be specified, as in cases of bacterial infections.[26] "Allergy" is rapidly becoming a huge wastepaper basket into which many diseases of unknown etiology are being tossed — a catch-all phrase like "eczema" or "rheumatism."

Periarteritis nodosa, a disease of unknown etiology, is now attributed to allergy or hypersensitivity because after a single positive exposure the patient died and autopsy showed arterial lesions similar to those of periarteritis nodosa. It is interesting to read the various editorial comments in the *Journal of the American Medical Association*. One of these states that periarteritis nodosa has generally been regarded as a rare disease, probably infectious, which almost always ends fatally and has rarely been diagnosed in vivo.[27] The chief histologic feature is a necrotizing lesion on the arterial wall with a surrounding inflammatory reaction. The diagnosis is difficult except in the rare cases that exhibit the characteristic subcutaneous nodules with the characteristic histologic changes in the blood vessels. Periarteritis nodosa has been attributed to syphilis, to a filterable virus, to various infections, to toxic injuries and to disease of the central nervous system. Gruber was among the earliest investigators to suggest that the condition was due to hypersensitivity.[27] The recent observations of Rich[28] and of Rich and Gregory[29] add support to this theory.

In 1942 Rich[28] reported autopsies on 5 patients who had had serum sickness shortly before death, in all of whom vascular lesions characteristic of periarteritis nodosa were demonstrable. None of the patients had any symptoms suggestive of periarteritis prior to the acute terminal illness, and all the vascular lesions were fresh. Similar vascular lesions were demonstrated in 2 patients who had had reactions to sulfonamide therapy.[30] Rich concluded that vascular lesions of the periarteritic type can be a manifestation of the anaphylactic type of hypersensitivity.

In the following year Rich and Gregory[29] reported the experimental production of similar lesions. Rabbits were sensitized with one or more large doses (10 cc.) of horse serum. All the animals showed on skin test the immediate anaphylactic

type of hypersensitivity, some developing Arthus reactions with necrosis. They were sacrificed at periods ranging from seventeen to twenty-six days, and the majority showed arteritic lesions characteristic of various stages of periarteritis nodosa. In an extension of this experiment the authors[31] found in the hearts of 11 of 36 similarly sensitized rabbits lesions that reproduced closely the five supposedly pathognomonic features of acute rheumatic carditis. Caution in interpreting these experiments is suggested by the reports of periarteritis developing in rats and dogs made hypertensive by clamping of the renal artery[32] or by wrapping of the kidney in silk.[33]

Another editorial states that the function and purpose of the allergic reactions are receiving close attention and that some attempt is being made to apply the result of laboratory experiments to patients.[34] The increased understanding of tissue reactions is a step forward. Concerning the allergic subject, however, it is not yet certain that the variation from the normal depends on anything more than a quantitative change.

An interesting clinical entity was described in 1932 by Loeffler. Miller[35] reported a case and stated that only 4 such cases had been reported in this country. The most important criteria for diagnosis, he asserted, are the symptoms and signs of pulmonary disease, the extent and character of pulmonary involvement, the transient character of the pulmonary shadows, eosinophilia and seasonal and sex variation. X-ray examination usually reveals a more extensive pulmonary involvement than was suspected from the clinical examination. The eosinophil count usually ranges between 15 and 35 per cent but has in some cases exceeded 60 per cent. The pathology of this disease is unknown, since no clear-cut fatal case has come to autopsy. The etiology of the disease is also uncertain. Most authorities describe the syndrome as an allergic response of the pulmonary tissue that may be induced by various allergens.

There must have been deaths later from this disease, for it is stated that the changes in the few cases examined after death appear to support the allergic explanation.[36] It is further pointed out that granulomatous processes in other organs, such as eosinophilic granuloma of bone, may also be allergic.[37]

In Weidman's excellent article on eosinophilic granulomas of the skin he considers their relation to Loeffler's syndrome. The journals of tropical medicine are outstanding in their reports of this disease because animal parasites (ranging from ascaris to ameba) are the occasion for the eosinophilia; Hodes and Wood[38] called it "tropical eosinophilia." Indeed, the injection of extracts of ascaris has proved the eosinophilogenous role of these parasites through the mechanism of allergy. The interstitial tissue (not the bronchi) is the shock organ.[39] Animal parasites, however, are not always demonstrable, notably in the cases in Palestine and those in which cutaneous manifestations were associated. Cutaneous involvement has been established by Lyon and Kleinhaus,[40] who reported 20 cases in Jerusalem in six months, although several patients did not exhibit pulmonary lesions. They cited other authors who spoke of "eosinophilic erythroedema," "eosinophilic disease with cutaneous manifestations" and eosinophilia in the sternal bone marrow in addition to the other lesions. Substantially, the dermatosis is a diffuse erythema multiforme perstans in large patches, affecting both the skin and the oral mucosa, and often migrating. In any event, a new message has come to dermatologists. Patients with persistent erythema multiforme lesions (including migrating ones) demand study regarding the possibilities of Loeffler's syndrome.[41, 42] Pujol[43] reports a case with dermatitis in Brazil.

I believe that if physicians keep this disease in mind many cases will be found. Within six months I have seen 2 cases that suggested it. The biopsy in each case showed no eosinophilia. The first patient was a three-year-old girl with a history of a more or less generalized eruption of three weeks' duration. The eruption consisted of raised, circinate plaques involving the arms, lower trunk and legs. Superimposed on several of the plaques were vesicles and small bullae. The patient also had a history of frequent asthmatic attacks and showed pediculosis of the scalp. The white-cell count was 17,500, with an eosinophil count ranging around 24 per cent. X-ray examination of the chest showed extensive mottling.

The second patient, a twenty-three-year-old man, was admitted to a tuberculosis sanatorium because of an x-ray diagnosis of tuberculosis. Repeated x-ray examination suggested sarcoid. Six weeks later the x-ray findings were essentially negative. The first examination revealed a half-dollar-sized erythematous wheal on the lower portion of the chest. This persisted, and three weeks later similar lesions appeared on the left arm, forehead, abdomen, buttocks and thighs. A diagnosis of erythema multiforme perstans was made. Three months later the eruption had disappeared, leaving pigmented areas. Laboratory studies were negative except for a white-cell count ranging from 13,500 to 29,000. There was a persistent increase in the percentage of eosinophils, ranging at times from 20 to 55 per cent. Sternal puncture showed marked eosinophilia, and nasal polyps removed were markedly infiltrated with eosinophils. This case is interesting because it has been stated by some authors that the roentgenographic appearance of the process is often not unlike that of tuberculosis.[44]

Rheumatic Diseases

According to Campbell et al.[45] erythema multiforme and erythema nodosum are not specific lesions of rheumatic fever. The most frequent type of eruption is found on the trunk, upper arms and legs.

The lesions, which are macular and from 1 to 2 cm. in diameter (occasionally larger), appear as bright-pink circinate or gyrate areas. They become more prominent after a few minutes' undressed exposure and vary from day to day. Red, elevated, edematous plaques may be seen over the affected joints. The cutaneous lesions appear after the joint manifestations. Subcutaneous nodules attached to tendons, ligaments and fascia over the elbows, knees or other joints may remain for several weeks and suggest a severe infection. Purpura and urticaria are not infrequent findings. Skin lesions in rheumatic fever do not help in deciding when rheumatic activity ends; they are merely acute manifestations occurring in a persistent disease.

Perry[46] studied 112 patients — 38 males and 74 females. The material reviewed offers little support to the theory that erythema nodosum is a manifestation of acute rheumatic fever. Perry agrees with those who have held that erythema nodosum must be regarded as the result of a nonspecific reaction to a variety of infections or toxic agents and that it is not a specific disease. It is clear, however, that these agents give rise to the syndrome only in patients constitutionally predisposed to it.

The relation between psoriasis and arthritis appearing before, during or after the appearance of the psoriatic lesions is a well established finding. The arthritis may respond to proper treatment of the psoriasis.

In a recent article Mallory[47] cites the hypothesis advanced by Rich that the lesions of periarteritis nodosa and rheumatic fever are the result of anaphylactic hypersensitivity.[31]

Sargent[48] reports 3 cases of Reiter's syndrome, the etiology of which is completely unknown. This disease of dramatic proportions is characterized by extensive lesions of the joints, mucous membranes and skin. It is exceedingly protracted in its course sometimes reactivating after prolonged periods of remission, but tending to spontaneous recovery. It is utterly refractory to all known treatment, except perhaps as it may be mildly benefited by such indirect stimulative and supportive methods as local physiotherapy, fever therapy and whole-blood transfusions.

Reiter[49] first described this disease as being characterized by arthritis, urethritis and conjunctivitis not caused by gonorrhea. In 1942 Bauer and Engleman[50] first reported it in the American literature with their series of 6 cases. In 1944 Lever and Crawford[51] followed with a report of 2 cases, the second of which (the only case so far reported in a female) left them in doubt regarding its proper classification.

Although in many cases the clinical picture is one of average chronic polyarticular arthritis associated with mild and fleeting inflammation of the mucosa of the eye and genitals, when Reiter's disease is in full bloom a low-grade fever is present, lesions of the buccal mucosa and of the epidermis occur, its mild conjunctivitis becomes an extensive iritis and keratitis, its arthritis settles in several joints and is of deforming proportions, sometimes ending in ankylosis, and its urologic manifestations extend to widespread superficial ulceration of the glans penis and even the urethral and bladder mucosa, causing discharge, pyuria and protracted severe cystitis. Yet the disease is completely devoid of any bacterial basis demonstrable by smear, culture, skin test and complement-fixation test or dark-field examination. Two patients whose cases were reported were attached to the same construction battalion, and their duties led to rather close association over periods of eight and nine months, respectively, prior to the beginning of the illness. The disease strongly suggests an infectious cause. Further study may prove that it falls into the ever-growing group of virus diseases. Idiopathic blennorrheal arthritis is suggested to give a fairly descriptive terminology to this little-known disease and to escape the use of a proper name.[48]

In 1945 Rosenblum[52] reported 10 cases of Reiter's syndrome in personnel of the United States Navy, of which 5 arose in the South Pacific and 5 in the United States. One patient had a widespread, acute skin eruption resembling erythema multiforme.[52] I recently treated a severe case at the United States Public Health Hospital in Brighton. The patient, a young man who had conjunctivitis, urethritis and arthritis, presented lesions in the axillary and genitocrural regions consisting of small bullae. Vesicles and bullae appeared on the palms and soles, and the eruption later became a dermatitis exfoliativa with complete loss of hair. The skin and hair became normal in several months, with complete recovery, and there was no limitation of joint motion.

Metabolism

Numerous articles describing cutaneous manifestations of nutritional disturbances have recently appeared. In 1888 Gee published a classic description of idiopathic steatorrhea. In this affliction skin lesions are frequent and diversified; they may be pigmented patches, psoriasiform plaques, eczematous areas or pustular dermatitides. The combination of skin lesions, infantilism, anemia, osteomalacia, tetany, dilatation of the colon and fatty stools may be found in a patient suffering from celiac disease.[54]

There are four centuries intervening between the scurvy of the days of the Crusaders and the beginning of our present-day knowledge of the subject. Impetiginous eruptions were described nearly two hundred years ago, in 1763. Cutaneous avitaminosis in children has been reviewed by Ormsby et al.,[55] who state that the lesions due to vitamin A deficiency are similar to those found in adults, except for lichen spinulosis, which is found exclusively in children and

is characterized by minute papules situated over the pilosebaceous follicles, each with a projecting horny spinule. Pellagra is usually less marked in children. With all the literature on avitaminosis one wonders why more skin diseases from nutritional deficiencies were not reported from concentration camps. Parasitic diseases were frequent, but pictures of starved prisoners showed no evidence of cutaneous manifestations. Some cases of pellagra, however, were reported. Among war prisoners in Java and Sumatra, the localization of true pellagra pigmentation was usually on the back of the hands and the feet and on the dorsal skin; sometimes the hair turned from spotless black to gray in three months.[56]

Chavarria et al.[57] report that hair disturbances have been noted in children, especially in the severe forms of vitamin A deficiencies, pellagra, riboflavin deficiency (cheilosis), nutritional edema, beriberi and the mixed forms of these general groups. They exhibit characteristic, associated changes in the hair, including both loss — diffuse or especially pronounced in the frontal area — and depigmentation. Biotin is thought but not proved to accelerate over other therapies the return to normal growth and pigmentation of the hair.[57] In the Medical Survey of Nutrition in Newfoundland note was made of a form of change in the hair — namely, a dry, lackluster hair, so-called "staring hair."[58]

The subject of the relation between the so-called "rosacea keratitis" and cutaneous rosacea has been debated a bit acrimoniously. Ariboflavinosis due to the vitamin B_2 deficiency is well known. There is considerable disagreement among the ophthalmologists themselves and the dermatologists regarding ocular disturbances. This was stimulated by a paper published in 1939 on the effect of experimental riboflavin deficiency on corneal vascularization in rats.[59] In 1940, after observing the relief of excessive corneal vascularization in 36 patients, although only 9 showed some type of cutaneous disturbance, Johnson and Eckardt[60] made a diagnosis of rosacea keratitis. In June, 1940, Sydenstricker et al.[61] reported a careful survey of 45 patients in whom they found this same type of corneal vascularization, originating at the limbic plexus and extending centripetally, originally described by Bessey and Wolbach.[59] Sydenstricker labeled this eye disease dietary keratitis, but in November, 1940, Johnson[62] claimed rosacea keratitis to be identical with dietary keratitis. He reiterated this a year later[63] but admitted that rosacea is a poor term since the condition is not caused by acne rosacea. Subsequently, two papers, one by an ophthalmologist (Fish[64]) and another by a dermatologist (Wise[65]), and later a statement by Johnson[66] that the appearance of keratitis with acne rosacea is a coincidence, fairly well established the fact that the term "rosacea keratitis" is confusing and may have disastrous results. Ocular rosacea follows acne rosacea, and both are manifestations of the same disease and are not due to riboflavin deficiency. Ocular rosacea is due to staphylococcal infection and must be treated by local antiseptic applications. I have repeatedly seen patients with severe ocular rosacea who did not improve until the local therapy was applied to the skin.[26]

Metabolic diseases of the liver are manifested by cutaneous discolorations ranging from jaundice to the irregular, yellow-brown pigmentation of the lower legs and yellowish, wedge-shaped conjunctival thickenings near the cornea. In many liver diseases, multiple functions being affected, more than one alteration in the appearance of the skin is observed.

Brunsting and Mason[67] report that bullous eruptions simulating epidermolysis bullosa, in which the exposed surfaces are sensitive to light, occur in association with porphyria and may represent the presenting symptoms of the disorder. Porphyria is recognized as a rare familial, metabolic fault in which abnormal kinds and amounts of porphyrins, especially uroporphyrin, are excreted in the urine and feces. Granted that there is a certain correlation between bullous eruptions, photosensitivity and porphyria in animals and in man, it is not proved that the production of the bullae on the exposed surfaces is due to the photodynamic action of porphyrins in the skin. Cutaneous signs of epidermolysis bullosa, melanosis and hypertrichosis were present in a case of porphyria, presumably of the tardive congenital type, occurring in a fifty-eight-year-old woman who had hepatic dysfunction and a history of alcoholism.[67]

The most striking and familiar skin affection associated with liver disease is jaundice. Pruritus is often associated with jaundice. It may be present without visible jaundice and may be the first indication of liver disease or, conversely, need not be present even though the icterus is marked. Biliary disease has also been reported to be the cause of 48 per cent of 200 cases of urticaria studied by Menagh,[68] who states that treatment of the biliary disease cured the urticaria in 60 per cent of cases.

A frequent finding in patients with liver disease is that of angiomas (telangiectasia or "spider angiomas") appearing on the face, neck, upper portion of the chest, shoulders and arms. Bean[69] asserts that there is an increase in the estrogen content of the blood, owing to inability of the liver to detoxify or otherwise cause an inert estrogen to be formed. Spider angiomas in the acute stage of infectious hepatitis have occasionally been described.[70, 71] In a clinical study of Navy patients at the Rockefeller Hospital, approximately 30 per cent developed spider angiomas during the acute stage of the disease.[72] New spider angiomas usually signified a poor prognosis when they developed after the acute stage of hepatitis.[73]

The vascular "spider" (naevus araneus, spider telangiectasia, spider angioma, stellate naevus and so forth) is a bright-red lesion characterized by a

central point from which fine, hairlike branches radiate for a distance of about 1 cm. Vascular spiders are seen in healthy persons, alcoholic patients, pregnant women and patients with liver disease and in avitaminosis. There is a hereditary tendency in which the lesions are found scattered over the skin and in the mucous membranes — that is, hereditary hemorrhagic telangiectasia (Rendu–Osler–Weber syndrome).

Williams and Snell[74] have suggested that the tendency to vascular spiders is transmitted as a dominant trait in some persons and as a recessive trait in others. The characteristic appears to be dominant in hereditary hemorrhagic telangiectasia, whereas it is probably recessive when there is no definite familial tendency. Vascular spiders frequently antedate the symptoms and signs of hepatic disease by as long as fifteen to twenty years. Patek et al.[75] reported them in 48 of 63 patients with hepatic cirrhosis. In a more extensive study of 368 cases of cirrhosis, Ratnoff and Patek[76] described vascular spiders in 15 per cent and telangiectasia in 17 per cent. The vascular spiders associated with pregnancy appear between the second and fifth months, usually increase in size and number until nearly term and may disappear abruptly a few days after delivery. Another group includes persons who are known to have or are suspected of having vitamin-deficiency diseases.

Palmar erythema may be hereditary or acquired, the latter being most frequently associated with liver disease, but occasionally with pregnancy and possibly with vitamin deficiencies. Ratnoff and Patek[76] reported this condition in 16 of 386 patients with cirrhosis of the liver, with a review of 20 cases of erythema palmare hereditarium, 9 presented by Walsh and Becker[77] and 11 collected from the literature. In 4 of their cases the condition appeared during pregnancy and was associated with the development of lesions similar to naevus araneus on the arms, face, neck and upper part of the chest. The complete clinical picture has not previously been described. Capillary studies usually show a dilatation of the venous side of the capillary loops and the superficial venous plexus.[77]

When estrogens were injected into patients with liver disease, angiomas appeared. Palmar erythema, especially thenar and hypothenar, was observed. Many chronic alcoholic patients show hypertrophy of the breasts and partial loss of pubic and axillary hair.

The skin manifestation due to faulty prothrombin and fibrinogen production consists of purpuric lesions and bleeding from the mucosal surfaces, especially the nose. The syndrome of pernicious anemia may result from inability of the liver to store the EMF as a result of disease. The skin manifestations may be pallor, glossitis, icterus and graying of the hair. The liver converts provitamin A to vitamin A, which it stores. In severe chronic disease of the liver, vitamin A deficiency results, with xerophthalmia, a dry, harsh skin, follicular keratosis and acneform eruptions. Yellow discoloration of the skin due to carotenemia may be secondary to liver diseases.

A skin disease and liver disease may coexist with neither the primary source in many cases, as in hemochromatosis, in which there is bronzing of the skin, loss of hair, a pigment cirrhosis of the liver and diabetes. At the same time, liver disease may occur secondary to skin disease. Miyake et al.[78] have shown that there is a so-called "G substance" in the skin of animals with a dermatosis that, when inoculated into rabbits, causes pathologic changes (chiefly cloudy swelling) in the liver, kidney and testis. Iwama[79] noted hepatic and renal insufficiency in cases of exfoliativa erythroderma. One of his studies seems to offer evidence in favor of the liver as the cause of skin reactions. He concludes that there is a close relation between liver and skin disease.[80]

Altered metabolism of the liver may result in the formation of xanthomas. When one observes a yellow lesion or eruption on the skin, Melicow's[81] classification provides excellent data for a differential diagnosis. He states that xanthoma as a general term is inadequate and that the prefix "xanthic," which accurately characterizes the underlying condition, is more logical in most cases. According to his classification, the "pseudoxanthomas" or preferably the "xanthic granulomas" are manifestations of the reticuloendothelial response to destructive processes resulting in the accumulation of lipids and blood and are found in chronic inflammatory foci, neoplasm, possible selective response to an unknown irritant and when a metabolic disturbance is not demonstrable, such as xanthic granuloma palpebrarum (xanthelasma) or multiple xanthic granulomas, and possible response to repeated pounding, as in large arteries when cardiac hypertrophy and hypertension are present.[82] The xanthomatoses or preferably, the "xanthic lipoidoses" are primary or secondary. Xanthic neoplasms included "xanthoma" or xanthic fibroma and xanthocarcinoma. Lesions simulating xanthic entities because of similarity in color comprise pseudoxanthoma elasticum, traumatic fat necrosis of breast and so forth, fibrohemangioma, hemorrhagic bursitis, hemorrhage in a lipoma, myxoma or fibromyxoma and melanotic tumors.

The classification of xanthomas has been confusing, probably owing to deficient knowledge of the normal physicochemistry of lipoid metabolism. Various hormones in the pituitary and thyroid glands, the pancreas and the sex glands are closely linked with lipoid metabolism. Disturbances of utilization of or deficiencies of various vitamins are also factors. Hypercholesteremia and hyperlipemia may be seen in myxedema with lesions on the skin.

The exact etiology of the xanthomas is unknown; not all are associated with a hyperlipemia, and they may occur without liver disease. Montgomery,[83]

however, in a series of cases noted that cutaneous xanthomas (xanthoma tuberosum, xanthoma disseminatum and xanthelasma) are not infrequently seen in association with liver disease, especially in obstructive jaundice. There is usually a hyperlipemia with an increase in lecithin. Palmar lesions are frequent, often in association with lesions of the mucous membrane. Xanthomas often involute as the liver disease improves.

Eusterman and Montgomery[84] report the case of a woman of forty-eight who came to the Mayo Clinic in May, 1941, complaining of severe, refractory generalized intense pruritus, continuous aching pain and hyperesthesia, especially in both extremities, cutaneous yellow nodules. gastrointestinal disturbances, loss of weight and strength, yellowing discoloration of the skin and severe physical and nervous exhaustion. They stress the fact that cutaneous xanthomas and hyperlipemia occasionally occur in association with primary disease of the liver (so-called "xanthomatous biliary cirrhosis") and in association with hepatic disease that is secondary to obstruction of the common bile duct, especially as the result of postoperative stricture. In cases in which the hepatic disease is primary, the prognosis is generally unfavorable. It is more favorable in cases in which the underlying pathologic process is due to obstruction of the common bile duct.

Combes and Behrman[85] discuss xanthoma diabeticorum and present a review of 181 cases from the literature. They suggest the more appropriate title "xanthoma eruptivum." The essential clinical features of the disease consist of the sudden appearance of multiple reddish-brown papules and nodules vaguely resembling erythema multiforme at their onset. The distribution is extensive, and the sites affected in particular are the extremities, the trunk and the mucosas. The lesions start as lentil-sized translucent nodules, sometimes with a small central blister. The diseases reported as extracellular cholesterosis and pseudodiabetic xanthoma are in all probability variants of xanthoma eruptivum.

To add to the confusion, a new entity —eosinophilic granuloma — has caught the interest of clinicians. In 1923 the histogenesis of eosinophilic granuloma was described as an unknown entity. The lesions have a dull erythematous appearance. They appear first as macules and develop into nodules or patches of firm elastic consistence varying in size from a millimeter to several centimeters. The accompanying blood eosinophil count ranges from 2 to 55 per cent, with an average of 20 per cent, lasting from two months to fifteen years. The name implies that there is an infiltration of polynuclear and mononuclear eosinophils in the dermis, which may extend into the subcutaneous tissue.[86]

Johnson and Zonderman[87] report a case involving the frontal bone, with recovery following surgery and x-ray therapy. Jaffe and Lichtenstein[88] define eosinophilic granuloma as a "condition affecting one, several or many bones, but apparently limited to the skeleton, and representing the mildest clinical expression of the peculiar inflammatory histiocytosis also underlying Letterer–Siwe disease and Schüller–Christian disease." Green and Farber,[89] Mallory,[90] Jaffe and Lichtenstein[88] and others have shown that the underlying lesion of this disease is related to the lesions of Schüller–Christian's disease and those of Letterer–Siwe's disease, which represents the gravest (eosinophilic granuloma representing the mildest) expression of the same basic pathologic process, which appears to have a predilection for the hemopoietic system. When this "peculiar inflammatory histiocytosis" manifests itself in infancy in its severe and often fatal form — characterized clinically by fever, purpuric skin rash, rapidly progressive hypochromic anemia, enlargement of the spleen, liver and lymph nodes and destructive bone lesions — it is classified as Letterer–Siwe's disease (aleukemic reticulosis, nonlipoidal histiocytosis). In its more chronic and less severe form, occurring in childhood and early adult life, after the lesions of the soft tissues and the bones have undergone lipogranulomatous changes, and especially — although not characteristically — when the Christian triad of symptoms (calvarial defects, exophthalmos and diabetes insipidus) has developed, the disease is labeled Schüller–Christian's disease (lipogranulomatosis). Roentgenographically the lesions appear as radiolucent areas varying in size. In the skull they tend to be round and sharply defined and have a punched-out appearance.

Nanta and Gadrat were the first to use the full term "eosinophilic granuloma of the skin" in 1937. This term was applied to bone by Finzi in 1939. The syphiloid of cats was described as "la syphiloide du chat (granulome eosinophilique)" by Henry and Bory in 1937. On the basis that Nanta and Gadrat have priority, the characteristics in their case should serve as the type for eosinophilic granuloma of the skin. The earlier reports of the disease indicate that the authors arrived rather promptly at the conclusion that it was not a clinical or etiologic entity. Therefore, the term can be used with the utmost latitude in any dermatosis with extreme eosinophilia in the tissues. In any event, attention should be focused on newer factors in the life of the population that might bear an influence on its tissue, especially the hemopoietic ones. The sulfonamides, barbiturates, aminopyrin and ethyl lead must be thought of when the clinical history is being elicited. In Weidman's[41] cases only two opportunities were supplied for testing for the presence of fat in the skin. Lever,[91] alone, raised this subject; he found new lipid-laden histiocytes and foam cells in his sections. In Weidman's sections there was no evidence of such disintegration.

Troxler and Niemetz[92] report a case of generalized xanthomatosis with involvement of bone, lungs and cerebrum. The unusual complication of bilateral

spontaneous pneumothorax occurred in this case. In the discussion they mention Hand–Schüller–Christian's disease as being considered as craniohypophyseal localization of lipoid granulomatosis. They quote Green and Farber[89] in concluding that eosinophilic or solitary granuloma of the bone is one form of generalized xanthomatosis and not a new disease entity. These authors also describe Letterer–Siwe's disease or reticuloendotheliosis as the same pathologic process seen in Hand–Schüller–Christian's disease. Wherever there is reticuloendothelium there can be lipoid granulomatosis. Thus, the clinical symptoms produced depend on the tissues involved and the degree of involvement.

Several interesting papers reporting eosinophilic granuloma with cutaneous manifestations have appeared in the dermatologic literature.[91, 93, 94] Just as I had decided on the cutaneous picture of eosinophilic granuloma, I saw a case of Thannhauser's presenting yellow, xanthomatous plaques on the eyelids and a yellowish, saber-blade type of patch extending from the hairy margin to the vertex of the scalp, with multiple small, dark-brown macules on the extremities, with symptoms of cerebral involvement and with a positive biopsy from the femur.

Some believe that eosinophilic granuloma is merely a late stage of a xanthomatous process. Others regard the lipoid factor as a secondary development due to the infiltration of the lipoid material into the granulomatous tissue. Apparently there are several symptom complexes with individual cases showing characteristics of more than one group. These syndromes include xanthomatosus of the skin and mucous membranes, Hand–Schüller–Christian disease, Niemann–Pick disease, Tay–Sachs disease and Gaucher's disease. A hypercholesteremia may or may not be present. Xanthomatous nodules and plaques may appear in almost any tissue, occasionally with enlargement of the spleen, liver and lymph nodes. Therefore, when a physician sees a cutaneous yellow lesion he should consider it a cutaneous manifestation of a general disturbance until he proves otherwise. Xanthomas secondary to general pathologic conditions such as diabetes mellitus and jaundice tend to disappear with proper systemic therapy. Skin lesions, however, may be independent of other disease.

Niemann–Pick[95] disease, or acute idiopathic lipoidosis, is a rare congenital familial disorder of lipoid metabolism in which the blood and tissues become overloaded with lipids, chiefly the phosphatide lecithin. The disorder begins in infancy, usually in the first six months of life and nearly always before the age of one year. Pfändler[96] reviewed observations on 14 members of a family in which 2 brothers died with Niemann–Pick disease at the ages of twenty-nine and thirty-three years, respectively. These cases demonstrate that this disease is not exclusively a disease of infants and young children. A genealogical tree of the family illustrates diagrammatically the various forms in which Niemann–Pick disease became manifest. Pfändler regards the latent forms as possibly more frequent than is generally believed.

Gaucher's disease, the second related disease, is a rare familial constitutional disorder of metabolism. It was first described by Gaucher[97] in 1882. The two types — the chronic and the rare acute form — are characterized pathologically by an enormously hypertrophied spleen and an enlarged liver, each of which shows on microscopical examination an infiltration of cells peculiar to the condition. These distinctive cells vary in diameter from 20 to 40 microns, stain palely with eosin and are usually oval or polygonal. The typical eruption of Gaucher's disease is a brownish-yellow pigmentation or bronzing of the skin, more pronounced and of a deeper hue on the face, neck, forearms and hands.[98–100] The other common lesions of the skin are of the hemorrhagic type — that is, petechiae, ecchymoses and hemorrhagic furuncles.[101, 102] A diagnosis of Gaucher's disease is suggested by an enormous abdomen, bronzing of the skin and a hemorrhagic diathesis. The presence of Gaucher's cells in the biopsy material from a peripheral lymph node or a splenic puncture is positive proof of the diagnosis.[103]

Acute pancreatitis is accompanied by a pallor cyanosis or lividity of the face and a cold clammy skin. Intestinal infestations may announce their presence by pruritic symptoms and lesions varying from a perianal eczema to the giant wheal. Persistent diarrhea with dermatitis and some mental change complete the syndrome of pellagra.

Blood

Osler was one of the first to recognize the syndrome called polycythemia vera, splenomegaly, cyanosis (erythrosis) and plethora.[104] Strickler[105] states that there are two frequent cutaneous manifestations of polycythemia vera: a purplish redness of the gums due to a highly reduced oxyhemoglobin content of the blood and a papular, pruritic, urticarial eruption with surmounting vesicles or pustules occurring in crops, which later become bloody crusts. This has been called acne urticata polycythemia.

Klauder[106] previously described this entity in a patient who had typical signs and symptoms consisting of headache, hypertension, albuminuria, hepatosplenomegaly, vasomotor instability, flushing, dermographism, a high blood uric acid and occasional ecchymosis. Marsh[107] distinguishes between the cyanosis seen in anoxic diseases and the erythrosis present in this entity, in which there is often an increased oxygen content. Brown and Griffin[108] believe that cutaneous lesions may be due to multiple thrombi and conclude that the erythrosis is due to peripheral vessel engorgement.

Anemia has various skin manifestations — the soft, waxy, delicate skin of the victim of pernicious

anemia, the green-yellow tint of the sufferer from hypochromic anemia and the smoothness and shiny appearance of the tongue seen in dysphagic old women with the Plummer–Vinson syndrome.[109] Spoon nails are also noted in this disease.[110]

Ulcers of the legs are observed in sickle-cell anemia, exclusively in Negroes.[111, 112]

Infectious lymphadenosis may present a roseolar eruption resembling syphilis, and an accompanying positive serologic reaction may deceive the unwary physician. Dameshek and Grassi[113] reported the case of a young woman with severe purpura hemorrhagica accompanied by generalized lymphadenopathy and a marked lymphocytosis. Although the clinical picture resembled that of acute lymphatic leukemia, the character of the lymphocytes suggested infectious mononucleosis; this was confirmed by a strongly positive heterophil-antibody agglutination. When the bleeding became uncontrollable, splenectomy was performed and resulted in prompt recovery.

Urticaria may be present in acute infectious lymphocytosis.[114] Eosinophilia may be found in conjunction with diseases of the skin. Kirk[115] divides the causes of eosinophilia into five classes: intestinal parasites — nematodes and some cystodes; blood diseases — eosinophilic leukemia and Hodgkin's disease; skin diseases — dermatitis herpetiformis and pemphigus; allergic diseases — asthma, eczema and hay fever; and miscellaneous diseases —periarteritis nodosa, trichinosis and Loeffler's syndrome and those occurring after the ingestion of raw liver. A significant rise in the eosinophils is present in urticaria, the neurodermatoses, pemphigus, erythema multiforme bullosum, dermatitis herpetiformis, hydroa, herpes iris, herpes gestationes and rarely in psoriasis.[115]

The eosinophil has been called a histamine scavenger. I have seen a 97 per cent eosinophil count with a white-cell count of over 65,000 in a case of generalized dermatitis from mercury . The blood became normal with clearing of the rash. Perhaps further study of eosinophilia will reveal the etiologic factor in some bullous diseases.

Purpura has been reported as resulting from many different factors — heredity, avitaminosis, allergy, anaphylaxis, infection, drugs and physical anomalies. As knowledge of the relation of drugs, infection and certain other conditions to thrombocytopenic purpura increases, the disease is less often described as idiopathic. Infection as an exciting cause of purpura is mentioned in most discussions of the etiology of thrombocytopenia. The etiologic importance of localized infection in the throat has been emphasized by many writers. Thrombocytopenic purpura following angina was considered sufficiently rare to warrant report of a fatal case.[116] Freud and Greenberg[117] report the first case in which the initial injection of a pertussis vaccine was followed by a generalized purpura and angioneurotic edema involving parts of the body far from the site of the injection. Hampton[118] states that food allergy caused 2 cases of purpura of the Henoch type.

Rucks and Hobson[119] reiterate that purpura fulminans is with few exceptions found in children owing to a fulminating blood-stream infection. They have reviewed 101 cases.

It is stated that purpura following the use of drugs such as arsenic, sulfonamides, coal-tar derivatives and gold is fairly frequent.[120–122] Several excellent reviews on purpura have recently been published.[123–127]

In discussing a rare fatal case of Henoch–Schönlein's purpura, Moore[128] states that fibrosis of the liver, seen in this case, is not found in lupus erythematosus or periarteritis nodosa, which others considered in differential diagnoses.

The detection of the causative factor of a purpuric eruption necessitates careful history taking, physical examination and laboratory studies. Very few cases can be diagnosed from observation, and the services of an expert hematologist are usually required.

Although in the experience of some clinicians leukemia cutis is rare,[129] in the practice of the dermatologist it is frequent enough to keep the possibility of its occurrence ever present in his mind. A persistent pruritus always demands a thorough blood study in the young or the old. An acute ulcerative stomatitis may be the precursor of monocytic leukemia, and an acute exfoliating dermatitis may precede by months a change in the blood picture. I have seen so many varied types of eruption accompanying the leukemias that I hesitate to name any single eruption as being specific, for even in the tumor stage the lymphomas may all resemble one another histologically and repeated biopsies are often necessary for the final diagnosis. The nonspecific lesions may be wheals, extravasation of the blood, papules, vesicles (single or grouped), bullae or ulcerations. Herpes zoster is frequently associated with the lymphatic group. Within two months I saw a patient with a generalized herpes zoster and another with an exanthema indistinguishable from varicella. Specific lesions due to infiltration of the leukemic process in the skin are those producing erythroderma, nodules and tumors; the last may break down into ulcerations. Nodules appear most frequently on the skin. Many excellent reviews have been published on the oral and cutaneous manifestations of the leukemias.[130–145]

Jackson and Parker[146] state that the skin lesions of Hodgkin's granuloma are often encountered. Marked excoriations due to severe pruritus of the skin are perhaps the most frequent lesions. Generalized or, more rarely, localized pigmentation occurs aside from that due to radiation therapy. Herpes zoster, not infrequently of a hemorrhagic type and often leaving behind it an indurated scar, is not unusual. The more specific lesions are generally

nodular or ulcerated and may exist for a long time prior to unequivocal evidence of the disease elsewhere.[146] Generalized exfoliating dermatitis has been reported; Jackson and Parker[147] saw 1 patient with this complication. In the past year I have treated 2 patients with a generalized dermatitis due to Hodgkin's disease.

The clinician should bear in mind that any chronic skin disease, whether it starts as a simple scaly eruption, such as parapsoriasis or psoriasis, or a vesicular eruption, such as chronic eczema, may eventually terminate as a fatal lymphoma. Hodgkin's disease should always be suspected in a persistent dermatitis exfoliativa, even if there is no visible adenopathy. I have seen more cases in the last few years than in all my previous years of practice. A well known hematologist remarked that the sulfonamides may be a factor, but I have failed to find a history of the ingestion of this drug except in the case of erythroderma suspected of being Hodgkin's disease. Other authors have reported eruptions varying from ichthyosis to ulceration.[148–155]

(To be concluded)

References

1. Spector, B. Developmental principles as applied to clinical medicine. *Bull. New Eng. M. Center* **6**:180-183, 1944.
2. Cockayne, E. A. *Inherited Abnormalities of the Skin and Its Appendages*. 394 pp. London: Oxford University Press, 1933.
3. Lancaster, A. H. Estrogenic hormone therapy in sunlight eruptions of females. *South. M. J.* **32**:495-499, 1939.
4. Urbach, E., and Le Winn, E. B. *Skin Diseases, Nutrition and Metabolism*. 634 pp. New York: Grune & Stratton, 1946.
5. Danbolt, N., and Closs, K. Akrodermatitis enteropathica. *Acta dermat.-venereol.* **23**:127-169, 1943.
6. Wende, G. W. Epidermolysis bullosa hereditaria. *J. Cutan. & Genito.-Urin. Dis.* **20**:537-547, 1902.
7. Thannhauser, S. J. Hereditary ectodermal dysplasia of "anhydrotic type," with symptoms of adrenal medulla insufficiency and with abnormalities of bones of skull. *J. A. M. A.* **106**:908-910, 1936.
8. Cole, H. N. Congenital cataracts in sisters with congenital ectodermal dysplasia. *J. A. M. A.* **130**:894, 1946.
9. Carleton, A. Skin-disease and cataract. *Brit. J. Dermat.* **55**:83-98, 1943.
10. Thannhauser, S. J. Werner's syndrome (progeria of adult) and Rothmund's syndrome: two types of closely related heredofamilial atrophic dermatoses with juvenile cataracts and endocrine features: critical study with five new cases. *Ann. Int. Med.* **23**: 559-626, 1945.
11. Moehlig, R. C. Progeria with nanism and congenital cataracts in five year old child. *J. A. M. A.* **132**:640-642, 1946.
12. Frank, L. Von Recklinghausen's disease traced through five generations. *Arch. Dermat. & Syph.* **55**:109, 1947.
13. Thannhauser, S. J. Neurofibromatosis (von Recklinghausen) and osteitis fibrosa cystica localisata et disseminata (von Recklinghausen): study of common pathogenesis of both diseases. Differentiation between "hyperparathyroidism with generalized decalcification and fibrocystic changes of skeleton and osteitis fibrosa cystica disseminata." *Medicine* **23**:105-149, 1944.
14. Lange, K. Capillary permeability in myxedema. *Am. J. M. Sc.* **208**: 8-15, 1944.
15. Amersbach, J. C., and Kanee, B. Localized myxedema in association with hyperthyroidism. *Arch. Dermat. & Syph.* **49**:415-417, 1944.
16. Pillsbury, D. M., and Stokes, J. H. Circumscribed myxedema of skin. *Arch. Dermat. & Syph.* **24**:255-270, 1931.
17. O'Leary, P. A. Localized solid edema of extremities in association with exophthalmic goiter. *Arch. Dermat. & Syph.* **21**:57-70, 1930.
18. Sunseri, J. Elephantiasic papulonodular myxedema. *Arch. Dermat. & Syph.* **48**:70-74, 1943.
19. Eppinger, H. Torpide Hautgeschwüre als Symptome eines localen myxödems. *Klin. Wchnschr.* **10**:682, 1931.
20. Ebert, M. H., and Otsuka, M. Lichen planus with recurrent attacks associated with exacerbations of hyperthyroidism. *Arch. Dermat. & Syph.* **48**:446, 1943.
21. Weber, F. P. Notes on nature of cutis verticis gyrata (bulldog scalp) and cutis striata or cutis sulcata, and particularly on their occurrence in acromegaly. *Brit. J. Dermat.* **40**:1-11, 1928.
22. Quimby, W. A. Pancreas and its relation to psoriasis, eczema and certain other diseases of skin. *Am. J. Roentgenol.* **56**:58-66, 1946.
23. Urbach, E. Skin diabetes: hyperglycodermia without hypoglycemia. *J. A. M. A.* **129**:438-440, 1945.
24. Sheppard, I. M. Oral manifestations of diabetes mellitus: study of 100 cases. *J. Am. Dent. A.* **29**:1188-1192, 1942.
25. von Pirquet, C. Allergie. *München. med. Wchnschr.* **53**:1457, 1906.
26. Downing, J. G. Recent advances in cutaneous medicine. *Connecticut State M. J.* **10**:566-575, 1946.
27. Editorial. Periarteritis nodosa and hypersensitivity. *J. A. M. A.* **133**:620, 1947.
28. Rich, A. R. Role of hypersensitivity in periarteritis nodosa as indicated by seven cases developing during serum sickness and sulfonamide therapy. *Bull. Johns Hopkins Hosp.* **71**:123-140, 1942.
29. Rich, A. R., and Gregory, J. E. Experimental demonstration that periarteritis nodosa is manifestation of hypersensitivity. *Bull. Johns Hopkins Hosp.* **72**:65-88, 1943.
30. Rich, A. R. Additional evidence of role of hypersensitivity in etiology of periarteritis nodosa: another case associated with sulfonamide reaction. *Bull. Johns Hopkins Hosp.* **71**:375-379, 1942.
31. Rich, A. R., and Gregory, J. E. Experimental evidence that lesions with basic characteristics of rheumatic carditis can result from anaphylactic hypersensitivity. *Bull. Johns Hopkins Hosp.* **73**: 239-264, 1943.
32. Wilson, C., and Byrom, F. B. Vicious circle in chronic Bright's disease. Experimental evidence from hypertensive rat. *Quart. J. Med.* **10**:65-93, 1941.
33. Smith, C. C., Zeek, P. M., and McGuire, J. Periarteritis nodosa in experimental hypertensive rats and dogs. *Am. J. Path.* **20**:721-735, 1944.
34. Editorial. Significance of allergy in disease. *J. A. M. A.* **108**:1434, 1937.
35. Miller, H. Transitory lung infiltrations accompanied by eosinophilia: report of case. *New Eng. J. Med.* **232**:7-10, 1945.
36. Editorial. Allergic pulmonary reactions of Loeffler's syndrome. *J. A. M. A.* **133**:325, 1947.
37. Bagenstoss, A. H., Bayley, E. C., and Lindberg, D. O. N. Loeffler's syndrome: report of case with pathologic examination of lungs. *Proc. Staff Meet., Mayo Clin.* **21**:457-465, 1946.
38. Hodes, P. J., and Wood, F. C. Eosinophilic lung (tropical eosinophilia). *Am. J. M. Sc.* **210**:288-295, 1945.
39. Editorial. Transitory pulmonary infiltrations associated with eosinophilia — Loeffler's syndrome. *J. A. M. A.* **126**:837, 1944.
40. Lyon, E., and Kleinhaus, E. M. Eosinophilic disease with cutaneous manifestations associated with transitory pulmonary infiltrations (Loeffler's syndrome). *Acta med. orient.* **4**:144-149, 1945.
41. Weidman, F. D. Eosinophilic granulomas of skin. *Arch. Dermat. & Syph.* **55**:155-175, 1947.
42. Wright, D. O., and Gold, E. M. Loeffler's syndrome associated with creeping eruption (cutaneous helminthiasis): report of twenty-six cases. *Arch. Int. Med.* **78**:303-312, 1946.
43. Pujol, Alfredo, Jr. Síndrome de Loeffler. *An. paulistas de med. e cir.* **52**:321-325, 1946.
44. Serra, L. M. Löffler's syndrome: review of literature and report of case. *Bull. School Med. Univ. Maryland* **30**:11-31, 1945.
45. Campbell, A. D., Griffith, C. G., and Leake, W. H. Skin lesions of rheumatic fever. *U. S. Nav. M. Bull.* **46**:360-366, 1946.
46. Perry, C. B. Aetiology of erythema nodosum. *Brit. M. J.* **2**:843-847, 1944.
47. Mallory, T. B. Pathology. *New Eng. J. Med.* **236**:438-443, 1947.
48. Sargent, J. C. Reiter's syndrome. *J. Urol.* **54**:556-564, 1945.
49. Reiter, H. Über eine bisher unerkannte Spirochätinfektion (Spirochaetosis arthritica). *Deutsche med. Wchnschr.* **42**:1535, 1916.
50. Bauer, W., and Engleman, E. P. Syndrome of unknown etiology characterized by urethritis, conjunctivitis, and arthritis (so-called Reiter's disease). *Tr. A. Am. Physicians* **57**:307-313, 1942.
51. Lever, W. F., and Crawford, G. M. Keratosis blennorrhagica without gonorrhea (Reiter's disease?). *Arch. Dermat. & Syph.* **49**: 389-397, 1944.
52. Rosenblum, H. H. So-called Reiter's disease: triad of acute arthritis conjunctivitis and urethritis. *U. S. Nav. M. Bull.* **44**:375-378, 1945.
53. Short, C. L. Arthritis in Mediterranean Theater of Operations. III. Clinical description of infectious and other types of arthritis. *New Eng. J. Med.* **236**:468-473, 1947.
54. *Classic Descriptions of Disease*. Edited by R. H. Major. Third edition. 630 pp. Springfield, Illinois: Charles C Thomas, 1932.
55. Ormsby, O. S., et al. Round table discussion on skin diseases in children. *J. Pediat.* **25**:265-274, 1944.
56. Foreign Letter. Pellagrosis (dermoberiberi Castellani) among war prisoners in Java and Sumatra. *J. A. M. A.* **132**:347, 1946.
57. Chavarría, A. P., Goldman, L. Saenz-Herrera, C., and Cordero-Carvajal, E. Canities and alopecia in children associated with avitaminosis: preliminary report. *J. A. M. A.* **132**:570-572, 1946.
58. Adamson, J. D., et al. Medical survey of nutrition in Newfoundland. *Canad. M. A. J.* **52**:227-250, 1945.
59. Bessey, O. A., and Wolbach, S. B. Vascularization of cornea of rat in riboflavin deficiency, with note on corneal vascularization in vitamin A deficiency. *J. Exper. Med.* **69**:1-12, 1939.
60. Johnson, L. V., and Eckardt, R. E. Rosacea keratitis and conditions with vascularization of cornea treated with riboflavin. *Arch. Ophth.* **23**:899-907, 1940.
61. Sydenstricker, V. P., Sebrell, W. H., Cleckley, H. M., and Kruse, H. D. Ocular manifestations of ariboflavinosis: progress note. *J. A. M. A.* **114**:2437-2445, 1940.

62. Johnson, L. V., and Eckardt, R. E. Ocular conditions associated with clinical riboflavin deficiency. *Arch. Ophth.* **24**:1001-1005, 1940.

63. Johnson, L. V. Clinical ocular conditions associated with vitamin B complex deficiencies. *Am. J. Ophth.* **24**:1233-1240, 1941.

64. Fish, W. M. Acne rosacea keratitis and riboflavine (vitamin B_2). *Brit. J. Ophth.* **27**:100-103, 1943.

65. Wise, G. Ocular rosacea. *Am. J. Ophth.* **26**:591-609, 1943.

66. Conners, C. A., Eckardt, R. E., and Johnson, L. V. Riboflavin for rosacea keratitis, marginal corneal ulcers and catarrhal corneal infiltrates: laboratory and clinical studies. *Arch. Ophth.* **29**:956-967, 1943.

67. Brunsting, L. A., and Mason, H. L. Porphyria with epidermolysis bullosa: report of case of Tardive congenital type with demonstration of latent porphyria in sister of patient. *J. A. M. A.* **132**: 509-514, 1946.

68. Menagh, F. R. Etiology and results of treatment in angioneurotic edema and urticaria. *J. A. M. A.* **90**:668-671, 1928.

69. Bean, W. B. Note on development of cutaneous arterial "spiders" and palmar erythema in persons with liver disease and their development following administration of estrogens. *Am. J. M. Sc.* **204**:251-253, 1942.

70. Turner, R. H., Snavely, J. R., Grossman, E. B., Buchman, R. N., and Foster, S. O. Some clinical studies of acute hepatitis occurring in soldiers after inoculation with yellow fever vaccine, with especial consideration of severe attacks. *Ann. Int. Med.* **20**:193-218, 1944.

71. Bean, W. B. Cutaneous arterial spider: survey. *Medicine* **24**:243-331, 1945.

72. Labby, D. H., Kunkel, H. G., Shank, R. A., and Hoagland, C. L. Unpublished data.

73. Kunkel, H. G., and Hoagland, C. L. Observations on family epidemic of infectious hepatitis. *New Eng. J. Med.* **236**:891-897, 1947.

74. Williams, D. H., and Snell, A. M. Pulsating angioma (generalized telangiectasia) of skin associated with hepatic disease. *Arch. Int. Med.* **62**:872-882, 1938.

75. Patek, A. J., Jr., Post, J., and Victor, J. C. Vascular "spider" associated with cirrhosis of liver. *Am. J. M. Sc.* **200**:341-347, 1940.

76. Ratnoff, O. D., and Patek, A. J., Jr. Natural history of Laennec's cirrhosis of liver: analysis of 386 cases. *Medicine* **21**:207-268, 1942.

77. Walsh, E. N., and Becker, S. W. Erythema palmare and naevus-araneus-like telangiectases. *Arch. Dermat. & Syph.* **44**:616-630, 1941.

78. Miyake, I., Gyotoku, M., and Tanae, N. Experimentelle Studien über den Giftstoff der Dermatitishaut. III. Einfluss der Dermatitishautextraktes auf das histologische Bild von Leber, Niere und Hoden. *Jap. J. Dermat. & Urol* **42**:314-316, 1937.

79. Iwama, M. Über die Beziehungen zwischen Leberschädigung und Hauterkrankung: 9 Fälle von Erythrodermia exfoliativa generalisata. *Jap. J. Dermat. & Urol.* **47**:14-24, 1940.

80. *Idem.* Über die Beziehungen zwischen Leberschädigung und Hauterkrankung: immuno-biologische Studien über die Haut bei Injektion von Hepatotoxin- und Nephrotoxinserum. *Jap. J. Dermat. & Urol.* **49**:13, 1941.

81. Melicow, M. M. Xanthic lesions: report of four cases, including two of "xanthomatosis" of kidney. *J. A. M. A.* **105**:768-774, 1935.

82. Plewes, L. W. Nature and origin of xanthoma cell. *Arch. Path.* **17**: 177-186, 1934.

83. Montgomery, H. Xanthomatosis. III. Cutaneous xanthoma, especially in relation to disease of liver. *J. Invest. Dermat.* **1**: 325-351, 1938.

84. Eusterman, G. B., and Montgomery, H. Disorders of liver and extrahepatic biliary ducts associated with cutaneous xanthomas and hyperlipemia. *Gastroenterology* **3**:275-286, 1944.

85. Combes, F. C., and Behrman, H. T. Xanthoma eruptivum (xanthoma diabeticorum). *Arch. Dermat. & Syph.* **43**:927-942, 1941.

86. Buley, H. M. Eosinophil granuloma of skin. *J. Invest. Dermat.* **7**: 291-300, 1946.

87. Johnson, C. I., and Zonderman, B. Eosinophilic granuloma: report of case involving frontal bone. *Ann. Otol. Rhinol. & Laryngol.* **55**: 938-944, 1946.

88. Jaffe, H. L., and Lichtenstein, L. Eosinophilic granuloma of bone: condition affecting one, several or many bones, but apparently limited to skeleton, and representing mildest clinical expression of peculiar inflammatory histiocytosis also underlying Letterer-Siwe disease and Schüller-Christian disease. *Arch. Path.* **37**:99-118, 1944.

89. Green, W. T., and Farber, S. Eosinophilic or solitary granuloma (relationship to Hand-Schüller-Christian disease). *J. Bone & Joint Surg.* **24**:499-526, 1942.

90. Mallory, T. B. Pathology: diseases of bone. *New Eng. J. Med.* **227**: 955-960, 1942.

91. Lever, W. F. Eosinophilic granuloma of skin: its relation to erythema elevatum diutinum and eosinophilic granuloma of bone: report of case. *Arch. Dermat. & Syph.* **55**:194-211, 1947.

92. Troxler, E. R., and Niemetz, D. Generalized xanthomatosis with pulmonary, skeletal and cerebral manifestations: report of case. *Ann. Int. Med.* **25**:960-968, 1946.

93. Lewis, G. M., and Cormia, F. E. Eosinophilic granuloma: theoretic and practical considerations based on study of case. *Arch. Dermat. & Syph.* **55**:176-193, 1947.

94. Dobes, W. L., and Weidman, F. D. Granulomatous Hodgkin's disease of skin with extreme eosinophilia (eosinophilic granuloma of skin? *Arch. Dermat. & Syph.* **55**:212-221, 1947.

95. Niemann, A. Ein unbekanntes Krankheitsbild. *Jahrb. f. Kinderh.* **29**:1-10, 1914.

96. Pfändler, U. La maladie de Niemann-Pick dans le cadre des lipoïdoses. *Schweiz. med. Wchnschr.* **76**:1128-1131, 1946.

97. Gaucher, P. C. W. *De l'epithelioma primitif de la rate, hypertrophie idiopathique de la rate sans leucemie.* Paris thesis, 1882.

98. Anderson, J. P. Hereditary Gaucher's disease. *J. A. M. A.* **101**: 979-981, 1933.

99. Bovaird, D., Jr. Primary splenomegaly — endothelial hyperplasia of spleen — two cases in children — autopsy and morphological examination in one. *Am. J. M. Sc.* **120**:377-402, 1900.

100. Brill, N. E., and Mandlebaum, F. S. Large-cell splenomegaly (Gaucher's disease): clinical and pathological study. *Am. J. M. Sc.* **146**:863-883, 1913.

101. Brill, N. E., Mandlebaum, F. S., and Libman, E. Primary splenomegaly — Gaucher type: report on one of four cases occurring in single generation of one family. *Am. J. M. Sc.* **129**:491-504, 1905.

102. Hoffman, S. J., and Makler, M. I. Gaucher's disease: review of literature and report of case diagnosed from section of inguinal lymph gland. *Am. J. Dis. Child.* **38**:775-793, 1929.

103. Lane, Clinton W., and Smith, M. G. Cutaneous manifestations of chronic (idiopathic) lipoidosis (Hand-Schüller-Christian disease): report of four cases, including autopsy observations. *Arch. Dermat. & Syph.* **39**:617-644, 1939.

104. Osler, W. *The Principles and Practice of Medicine.* Revised by H. A. Christian. Thirteenth edition. 1424 pp. New York: D. Appleton-Century Co., 1940.

105. Strickler, A. Polycythemia with unusual eruption. *Arch. Dermat. & Syph.* **52**:172, 1945.

106. Klauder, J. V. Acne urticata polycythaemica. *Arch. Dermat. & Syph.* **38**:145-147, 1938.

107. Marsh, H. E. Report of fifteen cases of erythremia. *M. Clin. North America* **3**:741-755, 1919.

108. Brown, G. E., and Griffin, H. Z. Studies of capillaries and blood volume in polycythemia vera. *Am. J. M. Sc.* **166**:489-502, 1932.

109. Savilahti, M. On pathologic anatomy of Plummer-Vinson syndrome. *Acta med. Scandinav.* **125**:40-54, 1946.

110. Anderson, N. P. Syndrome of spoon nails, anemia, cheilitis and dysphagia. *Arch. Dermat. & Syph.* **37**:816-822, 1938.

111. Anderson, W. W., and Ware, R. L. Sickle cell anemia. *J. A. M. A.* **99**:902-905, 1932.

112. Cummer, C. L., and LaRocco, C. G. Ulcers of legs in sickle cell anemia. *Arch. Dermat. & Syph.* **42**:1015-1039, 1940.

113. Dameshek, W., and Grassi, M. A. Infectious lymphadenosis ("mononucleosis") and thrombocytopenic purpura: recovery after splenectomy: report of case. *Blood* **1**:339-342, 1946.

114. Yuskis, A. S. Acute infectious lymphocytosis in adult: review of literature and report of case. *J. A. M. A.* **132**:638-640, 1946.

115. Kirk, R. C. Causes of eosinophilia. *Internat. Clin.* **5**:219-233, 1942.

116. Carroll, K. M. Thrombocytopenic purpura following angina: report of fatal case with autopsy. *Illinois M. J.* **89**:121-124, 1946.

117. Freud, P., and Greenberg, W. B. Purpura induced by initial injection of pertussis vaccine. *Arch. Pediat.* **63**:157-165, 1946.

118. Hampton, S. F. Henoch's purpura based on food allergy: report of two cases. *J. Allergy* **12**:579-591, 1941.

119. Rucks, W. L., and Hobson, J. J. Purpura fulminans (Waterhouse-Friderichsen syndrome): case report. *Memphis M. J.* **19**:18-24, 1944.

120. Guevara, P. F., and Miranda, A. G. Postarsenical blood diseases. *Rev. leprol., dermat. y sif.* **1**:4245, 1944.

121. Gorham, L. W., Proff, S., Schwind, J. L., and Climenko, D. R. Thrombocytopenic purpura caused by sulfonamide drugs: report of 3 cases. *Am. J. M. Sc.* **205**:246-257, 1943.

122. Hertzog, A. J. Essential thrombocytopenic purpura. *Minnesota Med.* **28**:198-202, 1945.

123. Ayerza, L., Taboada, F., and Nino, S. Purpura abdominal de Henoch. *Arch. argent. de enferm. d. ap. digest. y de la nutricion.* **18**:211-215, 1943.

124. Conklin, S. D., and Shank, P. J. Thrombocytopenia purpura associated with exophthalmic goiter: review of available literature and case report. *Ohio State M. J.* **40**:47, 1944.

125. Woodward, T. E. Thrombocytopenic purpura complicating acute catarrhal jaundice: report of case, review of literature, and review of 48 cases of purpura at University Hospital. *Ann. Int. Med.* **19**: 799-805, 1943.

126. Madison, F. W. Present status of hemorrhagic diseases. *Wisconsin M. J.* **43**:688-692, 1944.

127. Morrow, W. J. Purpura following scarlet fever. *Arch. Pediat.* **62**: 255-258, 1945.

128. Clinico-pathological Conference. Purpura, arthritis, hepatomegaly and hepatic failure. *Am. J. Med.* **1**:551-561, 1946.

129. Robey, W. H., and Russell, G. G. Leukemia cutis: report of case with discussion of treatment by use of hormones. *New Eng. J. Med.* **236**:505-507, 1947.

130. Wile, U. J. Cutaneous manifestations of systemic disease. *Ann. Int. Med.* **5**:1103-1112, 1932.

131. Montgomery, H., and Watkins, C. H. Exfoliative dermatitis as manifestation of monocytic leukemia (Schilling). *Minnesota Med.* **21**:636-641, 1938.

132. Mercer, S. T. Dermatosis of monocytic leukemia. *Arch. Dermat. & Syph.* **31**:615-635, 1935.

133. Freeman, H. E., and Koletsky, S. Cutaneous lesions in monocytic leukemia: report of two cases with pathologic study. *Arch. Dermat. & Syph.* **40**:218-240, 1939.

134. Lynch, F. W. Cutaneous lesions associated with monocytic leukemia reticulo-endotheliosis. *Arch. Dermat. & Syph.* **34**:775-796, 1936.

135. Epstein, E., and MacEachern, K. Dermatologic manifestations of lymphoblastoma-leukemia group. *Arch. Int. Med.* **60**:867-875, 1937.

136. Paul, J. T., and Limazi, L. R. Specific cutaneous lesions in chronic myeloid leukemia: clinical significance. *Arch. Dermat. & Syph.* **45**: 897-905, 1942.
137. Hollander, L., Kastlen, G. J., Permar, H. H., and Schmitt, C. L. Myeloid leukemia with cutaneous manifestations. *Arch. Dermat. & Syph.* **29**:821-834, 1934.
138. Gates, O. Cutaneous tumors in leukemia and lymphoma. *Arch. Dermat. & Syph.* **37**:1015-1030, 1938.
139. Moloney, W. C. Clinical significance of oral lesions in acute leukemia. *New Eng. J. Med.* **222**:577-579, 1940.
140. Reach, C. A. Oral manifestations of leucemia. *Am. J. Orthodontics* **26**:901-907, 1940.
141. Loveman, A. B. Some cutaneous manifestations of systemic disorders. *New Orleans M. & S. J.* **95**:446-450, 1943.
142. Wile, U. J., and Holman, H. H. Generalized herpes zoster associated with leukemia. *Arch. Dermat. & Syph.* **42**:587-592, 1940.
143. Craver, L. F., and Haagensen, C. D. Note on occurrence of herpes zoster in Hodgkin's disease, lymphosarcoma, and leukemias. *Am. J. Cancer* **16**:502-514, 1932.
144. MacKenna, R. M. B., and Davie, T. B. Lymphatic leukemia with cutaneous manifestations. *Lancet* **1**:1196-1198, 1932.
145. Case Records of the Massachusetts General Hospital (Case 25492). *New Eng. J. Med.* **221**:906, 1939.
146. Jackson, H., Jr., and Parker, F., Jr. Hodgkin's disease. II. Pathology. *New Eng. J. Med.* **231**:35-44, 1944.
147. *Idem.* Hodgkin's disease: involvement of certain organs. *New Eng. J. Med.* **232**:547-559, 1945.
148. Shelmire, B. Hodgkin's disease of skin. *South M. J.* **18**:511-519, 1925.
149. Cole, H. N. Cutaneous manifestations of Hodgkin's disease. Lymphogranulomatosis. *J. A. M. A.* **69**:341-348, 1917.
150. Miller, H. E. Lymphogranulomatosis cutis: Hodgkin's disease. *Arch. Dermat. & Syph.* **17**:156-181, 1928.
151. Reimann, H. A., Havens, W., and Herbut, P. Hodgkin's disease with specific lesions appearing first in skin. *Arch. Int. Med.* **70**: 434-443, 1942.
152. Fox, H. Lymphogranulomatosis of skin in Hodgkin's disease. *Arch. Dermat. & Syph.* **2**:578-593, 1920.
153. Senear, F. E., and Caro, M. R. Ulcerative Hodgkin's disease of skin. *Arch. Dermat. & Syph.* **35**:114-128, 1937.
154. Glazebrook, A. J., and Tomaszewski, W. Ichthyosiform atrophy of skin in Hodgkin's disease: report of case, with reference to vitamin A metabolism. *Arch. Dermat. & Syph.* **50**:85-89, 1944.
155. Ronchese, F. Ichthyosiform atrophy of skin in Hodgkin's disease. *Arch. Dermat. & Syph.* **47**:778-781, 1943.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

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CASE 33501

PRESENTATION OF CASE

A sixty-seven-year-old man entered the hospital with the chief complaint of food sticking in his throat.

For four months he had had difficulty swallowing solid food. If he swallowed a large particle, it stuck and produced a burning sensation in the lower substernal region, and no more food could pass for a while. Induced vomiting relieved the block. Liquids and soft solids were easily swallowed. There had been no weight loss, pain, cough or hematemesis. He had been slightly hoarse for three weeks.

X-ray studies and esophagoscopy at another hospital had demonstrated a lesion of the lower esophagus, which was not further described.

Physical examination disclosed a Grade II apical systolic murmur and a slightly enlarged prostate.

The temperature was 98°F., the pulse 60, and the respirations 17. The blood pressure was 160 systolic, 70 diastolic.

Examination of the blood revealed a hemoglobin of 15.1 gm. and a white-cell count of 8000. The urine was normal, with a specific gravity of 1.027. The total protein was 6.3 gm. and the nonprotein nitrogen 29 mg. per 100 cc. An electrocardiogram showed changes consistent with coronary-heart disease.

X-ray examination demonstrated an essentially normal chest. A gastrointestinal series showed a 2-cm. area of narrowing in the distal portion of the esophagus. No ulceration was seen. No tumor mass was visible. There was herniation of a portion of the stomach through the diaphragm. The films were otherwise negative.

An esophagoscopy was not performed. On the eighth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. EDWARD B. BENEDICT: Difficulty in swallowing is a very serious symptom and may be produced in a number of conditions, including benign and malignant tumor, benign stricture, cardiospasm, peptic ulcer of the esophagus, esophagitis, chemical burn and foreign body.

At the age of sixty-seven years, with a four-month history of dysphagia beginning with difficulty in swallowing solid food, the presumptive diagnosis is carcinoma of the esophagus until proved otherwise. The fact that food stuck and produced a burning sensation in the lower substernal region indicates that the lesion was in the lower esophagus, and the burning sensation points a little more toward an inflammatory process such as ulcer or esophagitis with benign stricture than to a tumor or to cardiospasm. The relief of the obstruction by induced vomiting does not help very much in the differential diagnosis. That liquids and soft solids were easily swallowed merely indicates that the obstruction was not complete and does not aid very much in the differentiation of a benign stricture from a carcinoma. One would expect, however, that an annular carcinoma of four months' duration would have produced some difficulty in swallowing soft solids and would probably have resulted in some loss of weight. The absence of pain is definitely against a diagnosis of peptic ulcer of the esophagus and somewhat against that of acute esophagitis. Substernal burning, however, is closely akin to pain. A cough in esophageal disease is usually secondary to rather complete esophageal obstruction with

spillage of food material into the trachea. This may occur in advanced cardiospasm or the late stages of carcinoma. There is little in the history to suggest cardiospasm, which is usually a disease of younger persons and occurs intermittently, frequently with emotional factors prominent in precipitating the attacks. The absence of hematemesis is not particularly helpful, because even in the presence of large ulcers or cancers of the esophagus, bleeding may not be a prominent symptom, and what bleeding does occur may be in the form of melena.

The hoarseness of three weeks' duration suggests the possibility of a malignant lesion with pressure on the recurrent laryngeal nerve and paralysis of a vocal cord. The hoarseness, however, may have been an incidental finding and not related to the esophageal disease, but due to a laryngitis.

There is nothing in the history to suggest a chemical burn such as the ingestion of lye, nor is there any history of foreign body.

Physical examination and laboratory studies are not particularly helpful, but a normal hemoglobin suggests the absence of cancer and the absence of a bleeding lesion.

We are told by the radiologist that there is a hiatus hernia and 2-cm. area of narrowing in the distal esophagus, with no visible ulceration or tumor mass.

The differential diagnosis from the above discussion seems to boil down to a carcinoma of the distal esophagus and a benign stricture with or without peptic ulceration. The fact that no ulceration was seen does not mean that none was present, for small ulcers of the esophagus are notoriously hard to demonstrate by the x-ray. The absence of a tumor mass is somewhat against the diagnosis of carcinoma. We are not told whether the area of narrowing is irregular or whether the margins of it are smooth. Obviously, a smooth narrowing would be more suggestive of a benign stricture, whereas a nodular narrowing would suggest cancer. Smooth narrowings, however, should always be viewed with some suspicion, since there may be a relatively smooth annular carcinoma simulating a benign stricture.

On the whole, I vote for benign stricture of the lower end of the esophagus associated with esophagitis for the following reasons: burning sensation in the lower substernal region, no weight loss, normal hemoglobin, no evidence of nodularity by x-ray examination and the presence of a hiatus hernia as described on x-ray study.

It has been my experience that benign strictures of the esophagus quite frequently occur in association with hiatus hernia, duodenal ulcer or esophageal ulcer. In a study of 44 cases I found that the disease was relatively infrequent in women, and that it occurred usually in men over fifty years old. In the series reported the benign stricture was associated with hiatus hernia in 17 cases, with duodenal ulcer in 15 and with esophageal ulcer in 8.* All the patients had some esophagitis.

In the case presented herewith no esophagoscopy was performed, presumably because the surgeon planned to do a resection of the lower end of the esophagus, regardless of whether he was dealing with a benign stricture or with a carcinoma. This method of treating a benign stricture of the lower end of the esophagus is a debatable point, since the results of esophagoscopy and bouginage, a previously swallowed thread being used as a guide, are usually satisfactory. In my opinion esophagoscopy should be done in all these cases, and adequate biopsy obtained from the lumen of the stricture, to make absolutely positive that one is not dealing with carcinoma. Bougies may then be passed at regular intervals, and a major operation thus avoided. It must be remembered that patients with esophagitis and benign stricture may have a normal acidity, and that the usual operation of esophageal resection with esophagogastric anastomosis leaves the lower end of the esophagus even more vulnerable than before to the action of the acid gastric juice, thus leading to the possibility of further esophagitis with or without esophageal ulcer. The time for major surgery in a patient of this sort, sixty-seven years old, is, it seems to me, after conservative measures have failed.

Dr. Robbins, will you please help us with the x-ray interpretations?

DR. LAURENCE L. ROBBINS: Although I did not fluoroscope the patient, the films show a small hiatus hernia and approximately 2 cm. above the cardia of the stomach there appears to be a crater about 1 cm. in diameter. There is no evidence of a shelf, and no mass is seen either extrinsically or protruding into the lumen.

The remainder of the stomach and the chest show no evidence of tumor.

DR. BENEDICT: Dr. Robbins believes that there is probably an esophageal ulcer. The radiologist who did the fluoroscopy saw no ulceration. Naturally, it is impossible to be sure. My diagnoses are hiatus hernia, esophagitis, benign stricture of the esophagus and question of esophageal ulcer.

DR. RICHARD H. SWEET: One of the principal reasons for operating on this man was the fact that an esophagoscopy had been performed at another hospital by a competent endoscopist and that a biopsy specimen obtained at that examination had been reported as epidermoid carcinoma by the pathologist. Obviously, the history was not that of carcinoma because of its long duration. Also, the patient was actually able to swallow considerable food at the time we saw him even though he had had his trouble for a long time.

An exploration of the chest was therefore carried out, and at operation, although it was not ab-

*Benedict, E. B. Benign stricture of esophagus. *Gastroenterology* **6**: 328, 1946.

solutely certain that we were dealing with a benign lesion, it seemed more than likely that it was an inflammatory stricture with ulceration rather than carcinoma, although a small carcinoma superimposed on an ulceration in that region could exist without my being able to determine its presence by palpation and inspection alone. I have actually had that experience in just such a case.

This brings up an important point, which I believe should be mentioned: lesions of this sort, in my opinion, should be regarded with as much suspicion as the prepyloric ulcers of the stomach because as experience is accumulated with them, I am willing to predict that there will appear to be a correlation between the pre-existence of such a lesion and some cases of carcinoma, of about the same magnitude as that with prepyloric ulcer.

I therefore proceeded with a resection and an esophagogastric anastomosis.

Clinical Diagnosis

Carcinoma of esophagus; benign stricture with ulceration?

Dr. Benedict's Diagnoses

Benign stricture of esophagus, with (?) ulcer.
Esophagitis.
Hiatus hernia.

Anatomical Diagnoses

Peptic ulcer of esophagus.
Acute and chronic esophagitis.

Pathological Discussion

Dr. Benjamin Castleman: The specimen received in the laboratory showed a shallow ulcer 2 cm. in diameter whose margins were irregular but well defined and not indurated. Microscopically, the base of the ulcer was covered with a fibrinoid membrane characteristic of peptic ulceration. There was no evidence of carcinoma. The surrounding esophageal mucosa and muscularis were moderately inflamed.

Dr. Sweet: The patient made an exceedingly rapid and favorable convalescence. At the time he left the hospital he was eating a liberal solid diet with much more comfort than he had for years.

CASE 33502

Presentation of Case

First admission. A sixty-nine-year-old physician was admitted to the hospital complaining of slowing of the urinary stream and nocturia.

For several years the patient had suffered from increasingly severe nocturia, frequency and difficulty in starting the urinary stream. He had had diabetes for several years and was satisfactorily controlled on 8 units of protamine-zinc insulin daily.

Physical examination revealed a healthy-appearing, unusually well preserved man. The heart was of normal size, and a soft systolic murmur was heard at the apex. The abdomen was normal. Rectal examination disclosed a smooth, symmetrically enlarged prostate.

The temperature, pulse and respirations were normal; the blood pressure was 165 systolic, 90 diastolic.

Examination of the blood revealed a hemoglobin of 13.8 gm. and a white-cell count of 6100. The urine had a specific gravity of 1.020 and gave a + test for albumin and a negative test for sugar. The urinary sediment contained 10 red cells, 150 white cells and numerous bacteria per high-power field. The nonprotein nitrogen of the blood was 122 mg. per 100 cc. A blood Hinton test was negative.

X-ray studies showed normal kidney outlines, the left kidney being somewhat low. The ureters were not dilated. No unusual soft-tissue mass was present. A large amount of mottled calcification was seen in the region of the prostate. The walls of the pelvic vessels were calcified.

On the fourth hospital day cystoscopy showed marked trabeculation of the bladder but was otherwise not remarkable. A perineal prostatectomy with removal of 20 gm. of tissue was performed. Pathological examination revealed hyperplasia and chronic prostatitis.

Recovery was uneventful, and the patient was discharged on the nineteenth hospital day.

Second admission (six months later). The patient had felt well for the first three months following discharge, but then noted indefinite suprapubic discomfort and pain. The pain gradually became severer and seemed to be localized in the right lower quadrant. In addition he had a slight afternoon fever. He was nauseated once, but there was no vomiting or change in bowel habit.

During the week prior to admission penicillin was administered without much effect. On the day before re-entry the pain became so severe that three injections of morphine were required for relief. The pain during this attack radiated into the groins.

The temperature was 100.2°F., the pulse 115, and the respirations 20.

There was slight tenderness over McBurney's point, without spasm. No masses were palpable, and rectal examination was negative. The palpable remnant of the prostate was small and symmetrical, without nodules or tenderness. There was no costovertebral-angle tenderness.

Examination of the blood disclosed a hemoglobin of 12.6 gm. and a white-cell count of 18,100. Urinalysis showed a specific gravity of 1.028, a ++ test for albumin and a yellow-brown test for sugar. Ureteral catheter specimens showed 45 to 75 red cells and 1 white cell per high-power field. The non-

protein nitrogen was 29 mg., and the fasting blood sugar 380 mg. per 100 cc.

Retrograde pyelograms showed normal kidney shadows, and the pelves, calyxes and ureters were not abnormal so far as visualized. X-ray films of the chest disclosed a few linear streaks on the lower right and middle portions of the chest. A barium enema revealed numerous diverticulums in the sigmoid colon. The appendix did not fill, but on the following day a linear streak of barium consistent with the appendix was seen in the right lower quadrant. A cystogram showed several diverticulums of the bladder.

The patient's condition during the first week in the hospital remained unchanged. The diabetes was brought under satisfactory control with insulin. The tenderness in the right lower quadrant persisted, and there was a daily rise in temperature to 101 and 102°F. The tenderness was sometimes prominent along the brim of the pelvis and above the pubis, as well as in the right lower quadrant just medial to and below the anterior superior spine of the ilium. No tenderness or masses were found on further rectal examination. On the eleventh hospital day one observer felt a tender mass in the right lower quadrant, with pain radiating to the scrotum on pressure.

An operation was performed.

Differential Diagnosis

Dr. F. A. Simeone: This sixty-nine-year-old man, who had an operation for what was presumably an inflammatory mass, because the mass was tender, had fever, leukocytosis and an increase in the pulse rate. I believe that the problem is to decide the nature of this inflammatory mass.

In reviewing the history of the previous admission we come to the conclusion that this was an ordinary case of benign hypertrophy of the prostate gland and that the perineal prostatectomy had been satisfactory. The patient was relieved and went home after nineteen days. The only unusual point is that he had a nonprotein nitrogen of 122 mg. on that admission. The urine was infected, as manifested by the 150 white cells per high-power field. This, together with back pressure, must have led to a certain degree of renal insufficiency. The infection subsided quickly, for the surgeon considered the patient ready for operation on the fourth day of hospitalization. There were no complications after operation and no evidence that a malignant tumor in the gland was missed. He was relieved after this operation for a period of three months; during the second three-month period, however, he began to get into some kind of trouble that was unrelenting and progressive to a point where operation became necessary. He first noted indefinite suprapubic discomfort and pain, — rather nondescript symptoms, which could be accounted for by a number of different conditions, — but the pain gradually became progressively severer and began to be localized in the right lower quadrant. In addition, he had fever, suggesting that this was probably an inflammatory process. One immediately thinks of appendicitis, — pain in the right lower quadrant is acute appendicitis until proved otherwise, — but this was certainly a strange course for appendicitis to follow. The patient had symptoms for three months. The pain radiated into the right groin. One wonders about the explanation for that. Could this pain in the right lower quadrant have been the pain of, let us say, acute inflammation of the seminal vesicles? Sometimes that pain does radiate into the right lower quadrant and into the groin, but the rectal examination was described as negative. The tenderness in McBurney's point was localized, but without spasm, and no masses were felt over a period of three months. Acute appendicitis of that duration is extremely unlikely. We have the help of the definite statement that the remnant of the prostate was certainly not at fault at that time. There was no costovertebral-angle tenderness to suggest that this was a referred pain from the kidney and upper ureter. The urinalysis was abnormal, of course, in that it showed glycosuria and a ++ test for albumin. We know that the patient had diabetes. Perhaps, with this added infection, the diabetes had got somewhat out of control.

It would be interesting to know for the differential diagnosis what the cellular content of the urine was. We know that the urine from the kidneys was normal. One might expect 45 to 75 red cells per high-power field from catheterization of the ureters and kidneys, but it would be interesting to know how many white cells there were in the bladder urine.

Dr. George G. Smith: I am sure that there were a good many white cells. There was about 20 ounces of residual urine.

Dr. Simeone: It was grossly infected urine?

Dr. Smith: Yes; slightly cloudy.

Dr. Simeone: We have further evidence from the x-ray studies, and I shall ask Dr. Wyman to present the films.

Dr. Stanley M. Wyman: At the time of the first admission the intravenous pyelogram showed a rather diminished function of the kidneys. The left kidney can be outlined lying somewhat low with normal contour. The right kidney is poorly seen but not remarkable. The dye filling is inadequate in both kidneys. There is trabeculation of the bladder and a diverticulum on the left, and a larger, broader diverticulum on the right. There are some changes in the bone structure of the pelvis consistent with Paget's disease. There is calcification in the region of the prostate, which appears to be large. The second film is that of a retrograde pyelogram and shows good filling of the right kidney, with rather faint filling of the left. No abnormality is demonstrated in either kidney. The ureters appear normal.

DR. SIMEONE: Is the irregularity at this point explained on the basis of trabeculation, or can it be a different kind of filling defect?

DR. WYMAN: I think that the irregularity on the right border is probably a diverticulum. I cannot demonstrate it well in these films. We have later films of the bladder that show a definite diverticulum on the left and probably one on the right. At least one lies more on the superior border. This is the shadow of the appendix. The barium enema showed diverticulums throughout the sigmoid but no other gross lesion.

DR. SIMEONE: Are these shadows all in the appendix? Does it curve all the way around, or is this shadow in tissue other than the appendix?

DR. WYMAN: I believe that it curls as you suggest. I cannot be sure, however. I think that the appendix lies over the sacroiliac joint.

DR. SIMEONE: It is mentioned in the history that there were shadows in the lung field. I assumed that these were consistent with old atelectasis instead of malignant lesions.

DR. WYMAN: The lung fields show about three linear shadows, which can be focal atelectasis or possibly old infarcts. There is some prominence of the left cardiac border in the region where the pulmonary artery is expected to lie, which probably represents prominence of that artery. I see no evidence of destruction of the ribs or metastatic nodules in the chest.

DR. SIMEONE: The patient's condition changed while he was on the ward, and a palpable mass in the right lower quadrant was felt by at least one observer. It would be interesting to know whether this mass was felt to extend into the pelvis or whether the outlines could be clearly defined and localized in the right lower quadrant. There is probably no mention of that in the record. This mass was not felt by rectal examination, suggesting that it was probably out of the true pelvis.

I believe that with this information we might embark on a differential diagnosis of this inflammatory mass. First of all, could this mass have been entirely independent of the genitourinary tract? We have the information that the patient had diverticulums in the sigmoid, but there was no evidence of diverticulitis. Demonstrable diverticulums, of course, are fairly common in the general population, but they seldom produce trouble. Perhaps 1 out of 10 cases may develop diverticulitis and cause trouble for the patient. An inflammatory mass may result from diverticulitis, but one would expect it to be on the left side and not on the right, although if the sigmoid was very mobile it might appear on the right side. There is no evidence of such a position of the sigmoid in the examination by barium enema.

Could this have been a late result of acute appendicitis? This was certainly not the usual case of acute appendicitis. However, an acute inflammatory lesion in the appendix may be dependent on some other more chronic lesion in it. For example, the patient could have had a carcinoma in the appendix, with inflammatory changes about it, increasing in degree until a palpable mass was felt, or he may have had a carcinoid of the appendix. Both these lesions, particularly the former, are extremely rare but might explain this case. The radiation of pain was a little unusual unless we assume that the appendix was lying in the pelvis. The filling of the appendix by means of barium I consider evidence against its involvement in this process, although filling of the appendix has been observed in acute appendicitis.

Could the patient have had a diverticulum of the cecum? I think that the chances for that are remote, and I shall dismiss it for lack of x-ray evidence. There is no apparent intrinsic lesion of the cecum that might give rise to this inflammatory mass in the right lower quadrant.

Can we relate this mass to the disease of the genitourinary tract? In favor of that supposition is the fact that the patient had trouble with the genitourinary tract, and it would be satisfying to explain this lesion on the same basis. In favor, also, of connecting this disease with the genitourinary tract is the fact that diverticulums were demonstrated in the bladder by x-ray study. Were they seen by cystoscopy?

DR. SMITH: Yes; they were.

DR. SIMEONE: It is possible that one of the complications of diverticulums of the bladder developed, particularly if there was evidence of persistent infection in the bladder urine. The complications of diverticulums are well known. Frequently, stones develop in bladder diverticulums. Less commonly, tumors develop in bladder diverticulums. Finally, such diverticulums may develop peridiverticulitis, with extension into the extraperitoneal pelvic tissues and sometimes actual rupture into the peritoneal cavity, leading to general peritonitis. Against the supposition that this lesion was connected with the disease of the bladder is the fact that no tenderness was elicited by rectum. If this had been an extension of inflammation from the bladder diverticulitis one would expect to feel some tenderness in the right side on the pelvic floor. Taking these possibilities together, the evidence is a little in favor of linking the present lesion with the genitourinary tract. The evidence is against the possibility of a disease referable to the gastrointestinal tract, and it is entirely possible that the patient developed a peridiverticulitis about this one diverticulum, with extension into the right lower quadrant leading to the mass that was palpated by the observer.

The next question that one might consider is whether this was an otherwise uncomplicated form of bladder diverticulitis or a tumor within the diverticulum that had grown and penetrated its walls. That is certainly a possibility, although we have no evidence for it except as a good guess. I

shall therefore make a preoperative diagnosis of right-lower-quadrant abscess due to extension of a peridiverticulitis of the bladder with a question of tumor within it.

DR. BRIANT L. DECKER: I saw this man several times. As I remember the history I thought that it was of shorter duration. He had severe pain associated with nausea of about five weeks' duration, although it is perfectly true that he may have had some discomfort before that. I thought that he had an appendiceal abscess. Just before he came to the hospital he was x-rayed outside, and the appendix was visualized. The note was made that the tip of the appendix was fixed and tender. I also thought that he was given streptomycin while he was in the hospital, and I think that the temperature came down to normal while he was on the streptomycin.

DR. SMITH: The first mention of the suprapubic discomfort was about three months before the patient died. I had seen him, and when I came back five weeks later the tenderness had increased. I was extremely puzzled why he had this fever and tenderness. I was the one who felt the mass, and I would say that it was small, about 2 or 3 cm. in diameter, just to the medial side of McBurney's point. There was nothing felt in the pelvis by bimanual examination. My next guess was that he had an infection of the iliac and aortic lymph nodes that was forming an abscess. He was seen by a surgical consultant, who first did not think that there was any indication for exploration but later did explore him. I think that if Ellery Queen were here he would get a lead from those x-ray films.

DR. TRACY B. MALLORY: Have you anything further to say, Dr. Wyman?

DR. WYMAN: I remember the answer and therefore cannot say anything.

CLINICAL DIAGNOSIS

Ruptured aortic aneurysm.

DR. SIMEONE'S DIAGNOSIS

Abscess of right lower quadrant from extension of peridiverticulitis of bladder.

ANATOMICAL DIAGNOSES

Ruptured arteriosclerotic aneurysm of right iliac artery, with retroperitoneal hematoma.
Arteriosclerosis, generalized.
Diverticulum of bladder.
Diverticulosis of sigmoid.

PATHOLOGICAL DISCUSSION

DR. MALLORY: This man was explored by Dr. Sweet, who found an aneurysm at the junction of the iliac artery and the aorta. Two days later the aneurysm suddenly burst, and the patient went into profound shock and died within a few hours of the episode.

At autopsy we found a massive retroperitoneal hematoma, which had dissected into the mesentery of the cecum and ascending colon and also had dissected beneath the parietal peritoneum around the lateral wall of the abdomen. The total hematoma was estimated to contain something in excess of 2 liters of blood. It seems probable that there had been minor leakage before the terminal episode to account for the attacks of acute pain.

The other findings were all historic landmarks and had nothing to do with the symptomatology. There was a slightly hypertrophied heart to go with the mild hypertension. There was a rather severe generalized arteriosclerosis but no dilatation of the aorta itself. The aneurysm was sharply limited to the right iliac artery. The sigmoid was full of diverticulums, none of which appeared inflamed. The bladder also contained numerous diverticulums that were not inflamed. There was a remnant of prostatic tissue left from the perineal prostatectomy. Have you anything further to add, Dr. Smith?

DR. SMITH: In the x-ray film the right ureter takes a peculiar course as it comes down over the brim of the pelvis. Knowing the answer it is easy enough to put two and two together. It is a slight departure from the normal.

DR. WYMAN: But it could be caused by a mass other than aneurysm?

DR. SIMEONE: A retroperitoneal abscess might do it as well as any other tumor.

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NEW DIRECTOR OF CHILDREN'S HOSPITAL

Dr. Guy W. Brugler, of Cleveland Heights, Ohio, has been named director of the Children's Hospital of Boston, succeeding Dr. Stanton Garfield, who has been acting director of the institution for the past few months.

Dr. Brugler has been assistant director of University Hospitals in Cleveland since 1939. He was on leave of absence during World War II for two years and was with the United States Army Fourth General Hospital in Australia and New Guinea, with the rank of lieutenant colonel. Subsequently, he was executive officer at the United States Army Woodrow Wilson General Hospital in Staunton, Virginia. His executive and administrative experience will be invaluable in carrying to completion the plans now underway at the Children's Hospital.

At the large teaching institutions it has long been evident that a mere knowledge of medicine is not enough for the head of what is actually a large corporation; nor is executive ability sufficient. Ideally, there should be a man who not only has a knowledge of medicine and is sympathetic with the needs of the professional staff but also has a sound business sense and administrative experience.

The plans of the trustees of the Children's Hospital are national in scope, and their fulfillment will do much to further the art and science of the medical care of this age group. The harmonious liaison between the professional and the executive sides is of the greatest importance, and it is believed that the trustees of the Children's Hospital, by wisely considering this fact, have made a good choice. We wish them all success and believe that in the appointment of their new director they have taken an important step in furthering their plans and ideals. The successful fruition of their project will result in great benefit, not only to greater Boston and New England but also to the country.

CHEMOTHERAPY OF TUBERCULOSIS

The successful use of sulfanilamide and its derivatives and the demonstration of the curative effect of penicillin for many types of infections have led, quite naturally, to renewed efforts to discover a true cure for tuberculosis. Sulfanilamide and those of its derivatives that have proved most successful against the common coccal and bacillary infections have been shown to be bacteriostatic in vitro but have not given encouraging results in the treatment of tuberculous infections. The studies of Rich and Follis[1] on the effects of sulfanilamide in experimental tuberculosis in guinea pigs, although they showed only minimal effects from this agent, have nevertheless laid the groundwork for the testing and screening of various agents for their therapeutic effects in this disease. Modification and standardization of the method by Feldman and his associates have brought out the effectiveness of a succession of chemicals of the sulfone group, including Promin, Diasone and Promizole, each of which gave promise

of only limited usefulness owing to the toxic effects of prolonged treatment with the large doses that are required for any therapeutic benefit.[2-5] The same methods and others involving infections in mice and even in chick embryos have since been used to establish the effectiveness of streptomycin in tuberculosis.

This is not the first or only period, however, when chemotherapeutic success, apparent or real, in the treatment of one type of infection or another has been accompanied by clinical trials and enthusiasm for the same or related agents in tuberculosis. A timely comprehensive and critical review of these and other aspects of the chemotherapy of tuberculosis was ably presented by Hart[6] in his Mitchell Lecture delivered last summer before the Royal College of Physicians in London. This lecture gives a chronologic account of the various agents and classes of agents that have been used during the past century. Although the lecturer's summaries and comments on some of the older types of therapy are of interest from the point of view of historical perspective, his analysis of the present status of the sulfones and of streptomycin and his outlook for the future are particularly significant and worthy of comment.

The experiences to date with the sulfonamides and related compounds are summarized somewhat as follows. They have a more deterrent effect on experimental tuberculosis in some species than any drugs previously tried. Although early established lesions may regress and even be resolved, the eradication of virulent infection, a necessary criterion in the acute or subacute disease of the hypersensitive guinea pig, has not been attained. In man the small number of cases treated, in the absence of simultaneous matched controls in most trials hitherto reported, has made the assessment of these drugs difficult, but the results do not appear so favorable as those in the guinea pig. This is explained either by a lower tolerance, with the result that adequate dosage is difficult to achieve because of the risk of objectionable symptoms or by the possibility that the type of disease is different or that the drug is altered in the body and thus inactivated. At best, some benefit in recent exudative lesions is attributable to these drugs, but no regression of the disease to quiescence or cure has been demonstrated. The clinical use of these chemotherapeutic agents is likely to be limited to local use or to their employment in combination with other substances, such as streptomycin.

A few years ago, interest in the chemical analysis of the mycobacteria had focused on their fatty structure. Because of this, emphasis was placed on a "lipophilic" approach to the chemotherapy of tuberculosis and search among antiseptics was centered on fat-soluble compounds. Hart properly points out that the results with water-soluble sulfones and with streptomycin emphasize the fact that the mycobacteria, despite their fatty structure, are apparently more susceptible to water-soluble antiseptics than to fat-soluble compounds; thus, the lipophilic approach to chemotherapy does not appear to be the only one, nor may it be the most fruitful.

There are many reasons for investigating the aromatic group of organic compounds for their possible use against tuberculosis. Some have been tested because of their relation to the sulfones, whereas others, such as the naphthaquinone derivatives, represent an attempt to interfere with bacterial metabolism through a structural similarity to hypothetical growth factors or growth stimulants of the vitamin K type. Others were studied in a search for growth inhibitors based on the increase in oxygen uptake by washed suspensions of tubercle bacilli produced by benzoic and salicylic acids and certain other aromatic compounds. Such investigations suggested that these or chemically similar substances may play a part in the normal oxidation of bacilli and that substituted benzoates and salicylates may interfere with the oxidation and so inhibit growth.* Certain dyes have also been used because of promising earlier results, and some of the acridine compounds have been tested because of their clinical value in protozoal and bacterial infections, whereas others were employed because they were wax-soluble.

None of these substances, however, have as yet given any evidence of efficacy, combined with safety, in human tuberculosis, although some of the clinical

*Several papers reporting encouraging results from the use of para-aminosalicylic acid, both in experimental infections and in clinical tuberculosis, have appeared recently in the Swedish literature. Studies of this compound are now also under way in some laboratories and clinics in this country.

trials are not yet complete. One compound, Calciferol, deserves particular mention, however; several French and British workers are noted as having observed good results in lupus vulgaris with this substance used in high dosage. Its exact mechanism of action has not been clarified, and these clinical results require confirmation. Although serious toxic effects have thus far not been reported, the possibility of calcific deposits in tissues must be watched.

A long list of antibiotics from natural sources, all of which have antibacterial action against the mycobacteria, is given. The sources of most of these antibiotics are species of Aspergillus and Streptomyces and organisms related to *Bacillus subtilis*. Among these agents, however, only streptomycin is obtaining a full therapeutic trial. Hart's evaluation of streptomycin is based on the early results. Experimentally, these seem to be much more favorable in guinea pigs than in mice. He believes that the effects in human beings justify cautious enthusiasm. The disadvantages are recognized, particularly the development of resistant strains during treatment, the necessity for prolonged therapy with large doses and the deleterious effect of an acid medium. For these reasons it is thought that other chemotherapeutic agents may prove to be more desirable for use in tuberculosis even should streptomycin justify its present hopes.

The chemical and antibiotic problems involved in the discovery of an effective chemotherapeutic agent, especially in tuberculosis, are ably discussed. Hart states that these two paths should ultimately converge — "for knowledge of the chemical structure of antibiotic substances may promote laboratory synthesis of active related compounds, while knowledge of the point of interference of such substances may give new information on the essential metabolism of the tubercle bacillus and lead to the purposeful creation of simpler synthetic antimetabolites." It is improbable, however, that success in chemotherapy will supersede all the tried and tested methods of control, acquired through the years, that are applied to the patient, to his family and to the community: rest can be expected to remain the foundation of treatment, surgical methods will be needed in certain types of cases, and the state of housing and of nutrition may be expected to continue to influence the trend of tuberculosis incidence and mortality. Hart concludes: "There are in the world perhaps between ten and twenty million sufferers from active tuberculosis. In order to reduce this inroad on world health we shall probably need most of the reasonable measures — social and economic, preventive and therapeutic — that we possess now or that we can acquire in the future. The attack will remain multiple; the tactics will change."

References

1. Rich, A. R., and Follis, R. J., Jr. Inhibitory effect of sulfanilamide on development of experimental tuberculosis in guinea pig. *Bull. Johns Hopkins Hosp.* 62:77-84, 1938.
2. Feldman, W. H., Hinshaw, H. C., and Moses, H. E. Promin in experimental tuberculosis: sodium p, p-diaminodiphenylsulfone-N, N'-didextrose sulfonate. *Am. Rev. Tuberc.* 45:303-333, 1942.
3. *Idem.* Therapeutic effects of disodium formaldehyde sulfoxylate diaminodiphenylsulfone in experimental tuberculosis. *Arch. Path.* 36:64-73, 1943.
4. Feldman, W. H., Hinshaw, H. C., and Mann, F. C. Promizole in tuberculosis: effect on previously established tuberculosis of guinea pigs of 4, 2'-diaminophenyl-5'-thiazolylsulfone (promizole). *Am. Rev. Tuberc.* 50:418-440, 1944.
5. Smith, M. I. Present status of research in chemotherapy of sulfonamides, sulfones, and related compounds in experimental tuberculosis. *New York State J. Med.* 45:1665-1672, 1945.
6. Hart, P. D. Chemotherapy of tuberculosis: research during past 100 years. *Brit. M. J.* 2:805-810 and 849-855, 1946.

A HUNDRED YEARS AGO

A revolution is very much needed in the manufacture of boots, the modern fashion of high heels being positively injurious to the frame work of the feet. If the foot is tilted from the top of a high-heeled boot, the toes are pressed forward, down an inclined plane, which distorts them, and leads to the formation of corns. In multitudes of young men, the pressure is so great forward, that the large toe joint and the little toe metatarsal articulations are affected with bunions, swell, and sometimes remain permanently enlarged and sensitive. All beauty and symmetry are forever lost, and to the last days of an extreme old age, a foot thus tortured into a state of disease will be both sore and distorted. Something might also be said of ladies' shoes, with high heels; but as they are victims to other and even worse effects on the chest from a determination to improve upon nature, their case is deferred for another occasion. — The introduction of a foreign body into the larynx, or trachea, is an accident generally attended with much terror and distress at the time, and often followed by symptoms of an alarming, and sometimes of a fatal, character. The occurrence of this accident is rendered more frequent, both by the heedlessness of children, and the foolish habit indulged in by many grown persons, of keeping pins, nails, and other like bodies, in the mouth. Dr. J. Mason Warren reports three interesting cases: the first was a child, who while in the act of laughing, drew a common garden bean, which she had in her mouth, into the

trachea; the second, a little boy, was suddenly seized with a choking and violent cough which he said was caused by a blacksmith's nail in his mouth; the third was a young woman who had been so unfortunate as to get a pin in her larynx, after undressing a child and incautiously putting the pins in her mouth as they were removed from its dress. As Dr. Warren says, a question always arises in the mind of the surgeon called to an instance of this kind as to the propriety of opening the windpipe and attempting the extraction of the foreign body without delay. If the nature of the symptoms be urgent, and immediate suffocation is threatened, there is no alternative but to proceed at once with operation. But if the violent paroxysm, which at first threatened life has subsided, and the substance has settled into one of the bronchial tubes, causing only occasional disturbance, the question becomes one of more difficult solution. Dr. W. avers, should another case of this kind occur to him, he should at once perform the operation of tracheotomy, and by a free use of ether, attempt to allay the irritability of the air passages, so as to allow a more easy exploration by instruments, than is generally afforded in the natural state. — At the annual meeting of the Boylston Medical Society, November 22d, 1847, the following gentlemen were elected officers for the ensuing year: Luther Parker, Jr., M.D., *President*; James W. Stone, M.D., 1st *Vice-President*; Daniel D. Slade, M.D, 2d *Vice-President*; Z. B. Adams, M.D., *Treasurer*; James C. Neilson, *Secretary*; and Edwin Leigh, *Librarian*. Drs. John Ware, Geo. Hayward, Enoch Hale, Z. B. Adams, G. C. Shattuck, Jr., John Homans, Jacob Bigelow, *Trustees*. — A law is needed in Massachusetts requiring every druggist, apothecary and wholesale dealer who desires to keep on hand drugs which may be deadly poisons, to procure a license to do so from the municipal authorities. Perhaps we may be censured for being over careful, and even whimsical in the scheme here proposed for protecting the people; but if so, we have a valid apology. Life is too precious to be subjected to the contingency of death when all danger might be avoided by a simple process. — Dr. C. A. Harris of Baltimore and Drs. Buckminster Brown, and W. T. G. Morton of Boston give us intelligence from Edinburgh of Prof. Simpson's discovery of chloroform as a substitute for ether in preventing the pain of surgical operations. In preparing and administering the substance to a patient, Dr. Morton obtained the polite assistance of Dr. E. R. Smilie, a person of some reputation in chemical science. A lady opportunely arrived at Dr. M.'s office for the purpose of inhaling ether, and having three teeth extracted under its operation. After inhaling ether and allowing its effect to pass away, about one ounce of freshly made chloroform was put upon the sponge previously freed from the effect of the ether, and administered by the usual method. The teeth were extracted without the knowledge of the patient; Dr. M. says the effects were similar to those produced by ether. The perfume of the new vapor is said to be not unpleasant, but the reversal, and the odor of it does not remain for any length of time obstinately attached to the clothes of the attendant, or exhaling in a disagreeable form from the lungs of the patient. Its exhibition is said to be accompanied by no sickness, vomiting, headache, salivation, or uneasiness of chest. — Extracted from the *Boston Medical and Surgical Journal*, December 1847.

R. F.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CANCER AND OTHER CHRONIC DISEASES

In the annual report of the Division of Cancer and Other Chronic Diseases certain figures pertaining to the cancer clinics are interesting. The attendance increased from 1927, the first year of the clinics, until 1940, when it reached a maximum of 5490 new patients, 32 per cent of whom had cancer. During the war years there was a decided drop in attendance, 1943 being the year having the smallest number. The trend has again been reversed, although in 1946 the total attendance of 4026 patients, with 35.4 per cent having cancer, is considerably less than that in 1940.

There has been an increase in the percentage of persons who delayed less than a month between the first appearance of symptoms and first consultation with a physician. In the period 1930–1935, 14 per cent delayed less than one month, and in 1946, 23 per cent. There was considerable difference in the delay depending on the location of the cancer.

In 1946 more patients came to the cancer clinics upon recommendation of physicians than in any previous year, the percentage being 88.8. Of the recommendations made at the clinics 88.5 per cent were carried out within a month.

There has been a great increase in the use of the Tumor Diagnosis Service. In 1926 a total of 2484 specimens were examined, and in 1946, 5264 specimens. In 1926, 371 physicians and 52 hospitals and in 1946, 809 physicians and 108 hospitals made use of this service.

During the war, teaching clinics decreased both in number and in attendance. Although they have not returned to their original extent, 20 clinics, with a total attendance of 781 physicians, were held in 1946.

Several of the tables from the annual report have been multigraphed and are available to the physicians of Massachusetts upon request to the Division of Cancer and Other Chronic Diseases, Massachusetts Department of Public Health, 100 Nashua Street, Boston 14.

THE CYTOLOGY TEST FOR CANCER

The Massachusetts Department of Public Health, in co-operation with the cancer clinics, has been carrying on an investigation of the cytology test for cancer of the uterus. This study, financed in part by the Commonwealth Fund, was inaugurated to determine the incidence of cancer of the uterus in women without gynecologic symptoms, whether this test is of sufficient value to warrant its continued use in the cancer clinics and whether it should be offered to all physicians in Massachusetts as another diagnostic service. An advisory committee for this study was appointed, consisting of Drs. Thomas Almy, John Fallon, Reginald Fitz, Maurice Fremont-Smith, Edward G. Huber, Joe V. Meigs and Shields Warren. Since the formation of this committee Dr. Almy and Dr. Huber have died.

The committee recommended collecting vaginal smears from women attending the cancer clinics, from both those with and those without gynecologic symptoms. Biopsies were obtained from as many patients with positive smears as possible. In some cases the smear diagnosis was confirmed; in others, it was not. It is desired that three years after the original smear these women have a repeat smear as well as a pelvic examination, to determine whether or not cancer is present. The follow-up smear should disclose whether the unconfirmed positive smears were falsely positive, as well as whether the negative smears were falsely negative.

The first half of the study has been completed, and preliminary indications are that the true rate of uterine cancer among symptom-free women lies between 2 and 4 per 1000, whereas that among women with gynecologic symptoms may lie between 75 and 100 per 1000.

Until the study is completed this diagnostic procedure will not be offered to physicians in the State, but so far as facilities permit, the examination of smears collected at the clinics will continue.

MISCELLANY

NOTES

Dr. Walter S. Burrage, of Boston, has been elected to the board of trustees of the American Allergy Fund, a national foundation for the support of scientific research and public education in the field of allergy. Dr. Burrage is assistant professor of medicine at Harvard Medical School and chief of allergy for the Veterans Administration, Branch No. 1. He is consultant at the United States Naval Hospital in Chelsea, physician at New England Deaconess Hospital and consultant at Massachusetts Eye and Ear Infirmary in Boston.

The American Allergy Fund has its headquarters in Cleveland, Ohio, and its president is Dr. Jonathan Forman, editor of the *Ohio State Medical Journal*. Dr. Sanford B. Hooker, of Boston University School of Medicine, is an associate of the fund and a member of its scientific advisory council, which is headed by Dr. A. J. Carlson, of the University of Chicago.

Dr. Samuel C. Harvey, formerly William H. Carmalt Professor of Surgery and chairman of the Department of Surgery, Yale University School of Medicine, was recently appointed professor of surgery with special reference to oncology (the study of tumors) at the School of Medicine. The new professorship is supported by grants from the National Cancer Institute of the United States Public Health Service and Mr. Robert E. Hunter, of Pasadena, California. Dr. Harvey will assume responsibility for stimulating investigation of the problem of cancer and for training medical students and physicians in the special problems involved in the diagnosis, treatment and care of patients with this disease.

His successor in the Department of Surgery is Dr. Gustaf E. Lindskog, formerly associate professor of surgery.

NORWOOD HOSPITAL

At a meeting of the senior staff of the Norwood Hospital on November 7, the following resolution was passed.

The Norwood Hospital Staff notes with regret the death of our late colleague, Dr. Louis Arkin.

Dr. Arkin was a member of the Associate Staff of the Norwood Hospital from March, 1945, to his death on October 1, 1947. In that time, he gained the respect and affection of the members by his ethical conduct and good fellowship. The Norwood Hospital Staff express deep regret at his passing and extend sincere sympathy to his bereaved relatives.

It is hereby resolved that a copy of this action be included in the records of the Norwood Hospital Staff and similar copies be sent to his nearest relative and published in the *New England Journal of Medicine*.

CORRESPONDENCE

RESTORATION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held October 17, it was voted to restore the registration to practice medicine in this Commonwealth to Dr. Morris J. Kupper, 961 Blue Hill Avenue, Roxbury, whose registration was revoked October 18, 1944.

H. QUIMBY GALLUPE, M.D., *Secretary*
State House
Boston

LEAD PAINT STILL A HAZARD

To the Editor: In the November 6 issue of the *Journal* there appears an editorial entitled "Epidemic Lead Poisoning." This title is supported by the facts presented and unquestionably explains how large numbers of infants and children may become victims of this disturbance at any one time, or as one might say, at any one exposure. The main point of the editorial is well taken and most assuredly merits the attention of the medical profession. However, it is unfortunate that the editorial places lead poisoning resulting from the ingestion of lead paint obtained from toys, cribs and so forth, and chewed by infants and young children in the background. Actually, this source of lead poisoning continues to be a real and not a mythical danger. A review of the cases of acute or chronic plumbism occurring among this age group will verify this statement. The manufacturers may not employ lead paint in painting their wares, but what type of paint does the average adult select in repainting cribs, toys and interior woodwork? There is adequate clinical evidence that he employs lead paint, and thus the young patients suffering from plumbism continue to present themselves at hospitals. They do not appear in epidemic proportions, but the total number over a given period proves startlingly high.

It therefore does not appear, as suggested in the editorial, that emphasis has sometimes been mistakenly placed by the medical profession on the source of lead in lead poisoning occurring among infants and children. One case of acute poliomyelitis does not make an epidemic, but its occurrence is disturbing to the parents and, as with lead poisoning, may prove disastrous if not fatal to the victim. It is the little things that count — even if it is only an old toy repainted with lead paint by a devoted parent.

R. CANNON ELEY, M.D.
300 Longwood Avenue
Boston, Mass.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Arthritis and Related Conditions. Edited by Theodore F. Bach, M.D., associate in medicine, Graduate School of Medicine, University of Pennsylvania, and chief, Arthritic Clinic, Abington Memorial Hospital, Abington, Pennsylvania. 8°, cloth, 472 pp., with 139 illustrations. Philadelphia: F. A. Davis Company, 1947. $6.50.

Deep Analysis: The clinical study of an individual case. By Charles Berg, M.D.(Lond.), D.P.M., fellow of the British Psychological Association, physician, British Hospital for Functional Mental and Nervous Disorders, and physician, Institute for Scientific Treatment of Delinquency. 8°, cloth, 254 pp. New York: W. W. Norton and Company, Incorporated, 1947. $3.50.

Osteotomy of the Long Bones. By Henry Milch, M.D., consulting orthopedist, Maimonides Hospital, and attending orthopedic surgeon, Hospital for Joint Diseases and Riverside Hospital, New York City. 8°, cloth, 294 pp., with 181 illustrations. Springfield, Illinois: Charles C Thomas, 1947. $6.75.

Textbook of the Nervous System: A foundation for clinical neurology. By H. Chandler Elliott, M.A., Ph.D., assistant professor of anatomy, Medical College of the State of South Carolina. With an introduction by Wilder Penfield, M.D. 4°, cloth, 384 pp., with 158 illustrations. Philadelphia: J. B. Lippincott Company, 1947. $8.00.

Cineplasty. By Henry H. Kessler, M.D., Ph.D., orthopedic and amputation consultant, Office of Vocational Rehabilitation, and member of New Jersey Rehabilitation Commission. With a foreword by Ross T. McIntire, Vice-Admiral (MC), U.S.N., the Surgeon General, United States Navy. 8°, cloth, 201 pp., with 199 illustrations. Springfield, Illinois: Charles C Thomas, 1947. $6.75.

NOTICES

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

A meeting of the New England Society of Physical Medicine will be held at the Hotel Kenmore, Boston, on Wednesday, December 17, at 8 p.m. Dr. Sidney Licht, editor of *Occupational Therapy and Rehabilitation*, will speak on the subject "Clinical Diagnostic Measures in Physical Medicine."

Physicians, physical therapists and nurses are invited to attend.

AMERICAN COLLEGE OF SURGEONS

Six sectional meetings of the American College of Surgeons will be held in 1948. The date and location of each meeting is as follows: January 20 and 21, Commodore Perry Hotel, Toledo, Ohio; January 26 and 27, Ansley Hotel, Atlanta, Georgia; January 30 and 31, Oklahoma Biltmore Hotel, Oklahoma City; March 1 and 2, Cosmopolitan Hotel, Denver, Colorado; March 15 and 16, Hotel Nicollet, Minneapolis, Minnesota; May 17 and 18, The Nova Scotian, Halifax, Nova Scotia. Fellows of the College, the medical profession at large and hospital personnel are invited. Each meeting will be two days in length and will include conferences for hospital personnel and sessions for the medical profession. The showing of medical motion picture films will begin each day's program at 8:30 a.m. There will be luncheon meetings each day and a dinner meeting on the first evening followed by a symposium on cancer. Panel discussions on scientific subjects, led by internationally known authorities in each field of surgery, will be held each morning and afternoon.

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Thursday, December 18

Friday, December 19

*9:00–10:00 a.m. Gastritis. Dr. Seymour Gray. Joseph H. Pratt Diagnostic Hospital.

*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

Monday, December 22

12:00 m. Clinicopathological Conference. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.

*12:15–1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

Tuesday, December 23

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

Wednesday, December 24

*12:00 m. Grand Rounds and Clinicopathological Conference (Children's Hospital). Amphitheater, Peter Bent Brigham Hospital.

*2:00–3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

*Open to the medical profession.

December 15–17. American Academy of Allergy. Page 602, issue o October 16.

December 16. Greater Boston Medical Society. Page 886, issue of December 4.

December 16. Experiences in the Pacific Area. Dr. Merrill Moore. South End Medical Club. 12:00 m. 554 Columbus Avenue, Boston.

December 17. New England Society of Physical Medicine. Notice above.

January–April. Thirteenth Postgraduate Seminar in Neurology and Psychiatry. Metropolitan State Hospital. Page 348, issue of August 28.

January 8. Dysmenorrhea. Dr. Joe V. Meigs. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

January 20 and 21. American College of Surgeons. Commodore Perry Hotel, Toledo, Ohio. Notice above.

January 26 and 27. American College of Surgeons. Ansley Hotel, Atlanta, Georgia. Notice above.

January 30 and 31. American College of Surgeons. Oklahoma Biltmore Hotel, Oklahoma City. Notice above.

February 6. American Board of Obstetrics and Gynecology. Page 242, issue of August 14.

March 28–April 4. American Association of Industrial Physicians and Surgeons, American Industrial Hygiene Association, American Conference of Governmental Industrial Hygienists, American Association of Industrial Nurses, Inc., and American Association of Industrial Dentists. Hotel Statler, Boston.

April 19–23. American College of Physicians. Page xiii, issue of July 31.

May 6–8. American Association for the Study of Goiter. Page xiii, issue of July 31.

May 17–20. American Urological Association. Hotel Statler, Boston.

May 18–22. American Association on Mental Deficiency. Copley Plaza, Boston.

May 25–27. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

District Medical Societies

FRANKLIN

January 13.
March 9.
May 11. Annual Meeting. Hotel Weldon.
All other meetings will be held at Franklin County Hospital.

MIDDLESEX EAST

January 21.
March 24.
May 12. Annual Meeting.
All meetings will be held at the Bear Hill Golf Club.

NORFOLK

January 27. Round-Table Discussion: Bleeding from the alimentary tract.
February 24. Obstetric and Gynecologic Night.
March 23. Harvard Night.

PLYMOUTH

January 15. Brockton Hospital, Brockton.
February 19. Toll House, Whitman.
March 18. Goddard Hospital, Brockton.
April 15. State Farm, Bridgewater.
May 20. Lakeville Sanatorium, Lakeville.

WORCESTER

January 14. St. Vincent's Hospital.
February 11. Worcester State Hospital.
March 10. Memorial Hospital.
April 14. Hahnemann Hospital.
May 12. Annual Meeting.